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ATYPICAL TYPHOID INFECTION *

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Typhoid fever with its well-known clinical and pathological picture may present itself in various atypical forms. Louis, in 1829, was apparently the first observer to note the disease without the usual intestinal lesions. Dittrich (1846), Lebert (1858) and Guyot (1870) contributed additional cases to the literature. Since the typhoid bacillus was not discovered and its etiological significance established by Eberth and Gaffky until 1880 and 1884, these early cases are open to question. Morre,[1] in 1880, reported a case of splenotyphoid with suppurative changes in the spleen and no demonstrable intestinal lesions. One year later Mader[2] reported a case of bronchotyphoid, while Church,[3] in 1882, reported three cases of extra-intestinal type. Among many others specifically described below, Vaillard[4] (1890), Phillips[5] and Beatty[6] (1897), Lartigau,[7] Richardson,[8] Howard[9] and Bryant[10] (1899), Turney[11] (1900),

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1. Morre: Enteric Fever without Disease of the Glands of the Ilium, Proc. Path. Soc., Dublin, 1880-82, ix, 26.
2. Mader: Tod. Bericht der k. k. Krankenanstalt Rudolf-Stiftung, Wien, 1881, p. 278.
3. Church: St. Barth. Hosp. Rep., 1882, xvii, 97.
4. Vaillard: De l'infection par le bacille typhique sans lèsions intestinales, La Semaine méd., 1890, No. 12, p. 96.
5. Phillips: Proc. Clin. Soc., London, Feb. 12, 1897.
6. Beatty: Enteric Fever without Intestinal Lesions, Brit. Med. Jour., Jan. 16, 1897, p. 148.
7. Lartigau: On Typhoid Septicemia with a Report of two Cases, One of Which Was a Typhoid Infection without Intestinal Lesions, New York Med. Jour., xx, No. 158; Bull. Johns Hopkins Hosp., 1899, x, 55.
8. Richardson: Boston Med. and Surg. Jour., 1899, p. 498.
9. Howard: Extra-Intestinal Inflammatory Lesions Caused by Typhoid Bacillus, Philadelphia Med. Jour., 1899, p. 402.
10. Bryant: Brit. Med. Jour., 1899, i, 776.
11. Turney: A Case of Typhoid Septicemia; necropsy, Lancet, London, Sept. 29, 1900, p. 940.

Opie and Bassett[12] (1901), McDaniel[13] (1902), Kaufmann[14] (1911), and Posselt[15] (1912) have reported cases, all being confirmed by bacteriological or serological examination.

Spleen.—Doglietti[16] has noted a case of so-called splenotyphoid with the spleen three times larger than normal and without intestinal or mesenteric node involvement. Blood-cultures were negative, but the typhoid bacillus was isolated from the roseola. Blumenthal[17] observed marked lymphoid hyperplasia of the spleen together with infarction and no specific intestinal lesions. In this group may be placed the cases of Griffon[18] (streptococcus mixed-infection), Monroe and Campbell[19] (perisplenic abscess and empyema), Melchior[20] (splenic abscess), Karlinski[21] (myomalacia cordis-infarct, etc.), Cheadle[22] and Guizzetti.[23]

Liver.—Some observers have stated that typhoid fever may induce severe parenchymatous changes together with cirrhosis, necrosis and atrophy, the condition simulating acute yellow atrophy. In 1865, Politzer noted in a four-months old baby acute liver atrophy with distinct hyperemia and enlargement of the solitary follicles and Peyer's patches, as well as the mesenteric nodes. Powell[24] has reported the case of a child with typhoid fever, hepatic cirrhosis and death from acute yellow atrophy. There was, however, no report of bacteriological or serological findings. Tecklenburg[25] observed a case of acute yellow atrophy presenting all the features of typhoid fever. Marked parenchymatous hepatic changes were noted by Bruno[26] in a 50-year-old woman with headache, delirium, Kernig's sign, splenic enlargement, muscular contractures and Widal positive 1:60. Necropsy showed engorgement of cranial sinuses, cloudy meningeal fluid and no intestinal lesions. Of McCrae's[27] series of 105 necropsies, one showed liver abscess. A number of observers have reported this lesion, among them being Meyer,[28] who, in 1911, reported

12. Opie and Bassett: Bull. Johns Hopkins Hosp., July, 1901.
13. McDaniel: Isolation of B. typhosus from Unusual Localizations. Cholecystitis, Meningitis and a Five Month Fetus, Jour. Am. Med. Assn., 1902, xxxvii.
14. Kaufmann: Lehrb. der spez. path. Anat., i, 504.
15. Posselt: Atypische typhusinfektionen. Typhus ohne Darmerkrankungen, Lubarsch and Ostertag's Ergebn. d. allg. Path., 1912, i, 237.
16. Doglietti: Gazz. med. di Torino, 1895.
17. Blumenthal: Ein Beitrag zur path. Anat. des Paratyphus, Centralbl. f. Bakteriol. (Orig.), 1903, xxxiv, 113.
18. Griffon: Bull. Soc. anat. de Paris, 1902, iv, 825.
19. Monroe and Campbell: Glasgow Med. Jour., 1904, lxii, 120; Glasgow Path. and Clin. Soc., May 9, 1909.
20. Melchior: Berl. Klin., 1909, No. 255.
21. Karlinski: Wien. med. Wchnschr., 1891, No. 11.
22. Cheadle: Lancet, London, 1897, ii, 254.
23. Guizzetti: Clin. med. ital., 1900, No. 6, p. 358.
24. Powell: Brit. Med. Jour., ii, 1086.
25. Tecklenburg: Inaug.-Dissert., Freiburg, 1902.
26. Bruno: Il Policlin., 1903, xxxiii, 1025.
27. McCrae: Osler's Modern Medicine, ii, 100.
28. Meyer: Wissensch. Verein der Aerzte Stettins, October, 1911.

the case of a 16-year-old boy. *B. typhosus* was isolated from the abscess. Intestinal lesions were absent.

Gall-Bladder.—Primary typhoidal inflammation of the gall-bladder is a recognized condition. In 1896, Kühnau[29] reported the following case: Female, aged 32 years. Died in the eighth week of the disease. Spleen moderately enlarged. Abscesses in the mesenteric nodes and kidneys. Suppurative cholecystitis. *B. typhosus* from the suppurative foci. Cushing[30] noted a case of gall-bladder infection and calculus formation with no previous history of typhoid fever. He discussed a possible agglutinative reaction in the bile and its relation to calculus formation. A young woman with typhoidal temperature and the symptoms of cholecystitis was seen by Besançon and Philibert.[31] Headache, diarrhea, roseola and splenic tumor were absent. Diazo positive. Widal positive 1:600. No note of bacteriological examination. A patient with suppurative hepatitis, cholecystitis and caval thrombosis was observed by Müller.[32] Widal positive 1:500. Additional case reports have been made by Morris,[33] Legendre,[34] Pratt,[35] Stewart,[36] Wilson,[37] Posselt[38] and Holmes.[39] Quenu and Duval[40] believe that many cases of benign and febrile icterus, Weill's disease, etc., are primary biliary infections with typhoid bacilli. Carlisle and Martin[41] observed a case of cholecystitis with calculi, necrosis and hepatic abscesses, and summarized fifty-two cases of primary gall-bladder infection.

Kidneys.—Typhoid fever may present itself with unusual renal symptoms — so-called nephrotyphoid. Thue's[42] case of acute hemorrhagic nephritis with ulcers of the colon and anus falls in this group. Numerous masses of typhoid bacilli were found in the renal tissues. Vanzetti[43] noted a 15-year-old girl with severe parenchymatous nephritis and uremia. Necropsy showed renal infarcts in which typhoid bacilli were

29. Kühnau: Berl. klin. Wchnschr., 1896, No. 30, p. 666.
30. Cushing: Bull. Johns Hopkins Hosp., 1898, ix, 91.
31. Besançon and Philibert: Bull. et. mém. Soc. med. d. hôp. de Paris, Nov. 29, 1901, p. 1230; Semaine méd., 1901, p. 396.
32. Müller, R.: Ztschr. f. Heilk., Prague, 1905, xxvi, Abt. f. path. Anat., p. 263.
33. Morris: Typhoid Infection with Primary Focus in the Gall-Bladder, New York Med. Jour., 1899, lxix, 122.
34. Legendre: Bull. et mém. Soc. méd. d. hôp. de Paris, Dec. 6, 1901.
35. Pratt: Typhoid Cholecystitis, with Observations upon Gall-Stone Formation, Am. Jour. Med. Sc., 1901, cxxii, 584.
36. Stewart: A Case of Primary Typhoid Cholecystitis with Calculi, Am. Med., 1904, vii, 1018; Proc. Philadelphia Co. Med. Soc., 1904, xxv, 109.
37. Wilson: Primary Typhoid Cholecystitis and Cholangitis, Jour. Am. Med. Assn., 1908, l, 1607.
38. Posselt: Ergebn. d. allg. Path., 1912, i, 265.
39. Holmes: New York Med. Jour., 1911, xciv, 315.
40. Quénu and Duval: Les angiocholites aigués, Soc. int. d. chir., 1909.
41. Carlisle and Martin: Proc. Path. Soc., New York, 1908, viii, 138.
42. Thue: Norsk. Mag., 1889, p. 272.
43. Vanzetti: Arch. p. le sc. med., 1902, xxvi, 59.

found. The spleen and intestines were normal. Flexner[44] has reported a case of typhoidal septicemia with focal renal abscesses from which *B. typhosus* was isolated. Bilateral renal abscesses have been reported by Krokiewicz.[45] Napier and Buchanan[46] have noted the persistence of hematuria for five months after infection and a similar case, though of shorter duration, was seen by Lesieur.[47] The bibliography further includes cases published by Kühnau,[29] Nattan-Larrier,[48] Scheib,[49] Monroe and Campbell[19] and Politzer.[50]

Lungs and Pleurae.—Typhoid bacilli sometimes produce pulmonary and pleural lesions, chiefly lobar and bronchopneumonia and pleural effusion. Bronchopneumonia appears to be the commonest of these lesions. Flexner[51] noted a case in which thrombosis of the pulmonary artery, pulmonary gangrene, pyopneumothorax and cholelithiasis were found. The intestines showed no evidences of typhoid fever. Examination revealed *B. typhosus* in the lungs, heart's blood, spleen, liver, kidneys and cerebrospinal fluid. Robinson observed a pneumotyphoid of the lobar type (cited by McCrae). Among fourteen cases with satisfactory cultures (cited by McCrea), typhoid bacilli in pure culture were isolated in two cases, typhoid and colon bacilli in two cases and these organisms with staphylococci in one case. Rau,[52] Ortner and Glaser[53] observed cases of pneumotyphoid with the sputum containing the specific organism. Several other observers have noted this condition. The literature in pneumotyphoid includes cases reported by Bruhl,[54] Castaigne,[55] Viola,[56] Grasset,[57] Bensis,[58] Du Cazal,[59] Kogawa,[60] Picchi,[61] Fallet and Bourdin-

44. Flexner: Jour. Pathol. and Bacteriol., 1895, iii, 202; Bull. Johns Hopkins Hosp., iv.
45. Krokiewicz: Typhusbazillen im Blute und Gruber-Widalsche Reaktion bei Pyämie., Wien klin. Wchnschr., 1908, p. 1633.
46. Napier and Buchanan: Glasgow Med. Jour., December, 1906.
47. Lesieur: Fièvre typhoïde à début brusque hématurique, Bull. et mém. Soc. méd. d. hôp. de Paris, Feb. 3, 1911.
48. Nattan-Larrier: Infections éberthienne et streptococcique, Compt. rend. Soc. anat., 1902, p. 827.
49. Scheib: Zur Kenntnis der typhösen Nephritis, Prag. med. Wchnschr., 1902 p. 257.
50. Politzer: Wien. med. Wchnschr., 1912, p. 207.
51. Flexner: Bull. Johns Hopkins Hosp., 1900, viii.
52. Rau: Ztschr. f. Heilk., Prague, 1904, xxv, 385. (Literatur über Pneumotyphus.)
53. Glaser: Deutsch. med. Wchnschr., 1902, p. 772. (Literatur.)
54. Bruhl: Gaz. hebd. de méd., 1897, No. 9.
55. Castaigne: Ibid., Gaz. hebd. de méd., No. 55.
56. Viola: Gazz. d. osp., 1899, No. 12.
57. Grasset: Rev. intern. de méd. et de chir., Paris, 1906, xvii, 121.
58. Bensis: Grèce méd., 1907, ix, 16.
59. Du Cazal: Bull. et mem. Soc. méd. d. hôp. de Paris, 1893, p. 243.
60. Kogawa: Jikwa Zasshi, Tokio, 1907, p. 248.
61. Picchi: Lo Sperimentale, 1899, 1900, liii, 299.

ière[62] and Bergasse.[63] Fewer examples of typhoidal pleuritis can be found. McNaughton and Rhea,[64] and Charin and Roger,[65] have seen acute hemorrhagic pleuritis; Sahli,[66] a serous pleuritis. Finley[67] summarized 2,200 cases of typhoid fever and found that nineteen presented evidences of pleurisy. He believes that this condition is induced in the majority of cases by the typhoid bacillus and that it is of benign character.

Brain.—The literature on meningo- and cerebro-typhoid includes a number of cases. Fernet[68] reported one case with strabismus and exophthalmos, but no diarrhea, roseola, etc. Section showed no splenic enlargement nor intestinal lesions, but *B. typhosus* was isolated from the cerebrospinal fluid. Merkens[69] noted another case in which the patient had been operated on for chronic purulent otitis media and soon afterward developed a temperosphenoidal abscess. There was no previous history of typhoid fever. Widal positive. Operation and death. No intestinal lesions. McCaskey and Porter,[70] Gurd and Nelles,[71] and Melchior[72] have recorded cerebral abscesses in which typhoid bacilli were found. Purulent meningitis cases have been reported by Norman and Rosenburger[73] and Stäubli.[74] Caussade and Phillips[75] have mentioned a case in which a "meningotyphus" was apparently superimposed on an old pachymeningitis. Bergé and Weissenbach,[76] Flexner, Lavenson,[77] and Norman and Rosenburger[73] isolated at autopsy *B. typhosus* from the cerebrospinal fluid. On lumbar puncture Stühmer[78] and Schwartz[79] each

62. Fallet and Bourdinière: Progrès med., 1911, xxvii.
63. Bergasse: Bull. Soc. méd. chir. de la Drôme, 1911, xiii, 162.
64. McNaughton and Rhea: Jour. Can. Med. Assn., Sept. 1912.
65. Charin and Roger: Presence du bacille d'Eberth dans un epanchement pleural hèmorrhagique, Bull. et mém. Soc. méd. d. hôp. de Paris, 1891, p. 185.
66. Sahli: Centralbl. f. Bakteriol., Ref., 1894, xvi, 651.
67. Finley: Jour. Can. Med. Assn., Sept., 1912.
68. Fernet: Bull. et mém. Soc. méd. d. hôp. de Paris, 1891, p. 361.
69. Merkens: Zentralbl. f. Chir., 1898, p. 1058.
70. McCaskey and Porter: A Case of Brain Abscess Due to Latent Typhoid Infection, Operation; Death from Cardiac Complication, Jour. Am. Med. Assn., 1903, xl.
71. Gurd and Nelles: Ann. Surg., 1908, i, 4.
72. Melchior: Centralbl. f. d. Grenzgeb. d. Med. u. Chir., 1911, Nos. 1-2.
73. Norman and Rosenburger: Purulent Cerebrospinal Meningitis Caused by the Typhoid Bacillus, without the Usual Intestinal Lesions of Typhoid, Am. Jour. Med. Sc., 1908, cxxxv, 240; Proc. Path. Soc., Philadelphia, 1908, xi, 52.
74. Stäubli: Deutsch. Arch. f. klin. Med., 1904, lxxxii, 90.
75. Caussade and Phillips: Bull. et mém. Soc. méd. d. hôp. de Paris, 1911, p. 867.
76. Bergé and Weissenbach: Bull. et. mém. Soc. méd. d. hôp. de Paris, 1911, No. 30.
77. Lavenson: Typhoid Meningitis without Other Lesions, Univ. Penn. Med. Bull., April, 1908.
78. Stühmer: München. med. Wchnschr., 1910, p. 357.
79. Schwartz: Med. Rec., New York, Oct. 29, 1910.

found the organism in one case. The former summarized the literature of eight cases in which during life the organism had been isolated. Cole[80] has suggested that serous meningitis due to typhoid bacilli is probably more common than is supposed. Further contributions to literature on meningotyphoid have been made by Vincent,[81] Bruno[26] and Picchi.[82]

Unusual Alimentary and Laryngeal Lesions.—Aberrant typhoidal ulcers have been found in the mouth, fauces, pharynx, larynx, esophagus, stomach, rectum and at the anus. Louis was the first to call attention to esophageal ulcers in typhoid fever. In Koranyi's clinic, Vas[83] noted in a series of 322 typhoid patients eight with specific pharyngeal and laryngeal lesions. In ten examinations Besson[84] found typhoid bacilli six times in the tonsils. In an epidemic, Cappellari[85] observed five severe cases with characteristic tonsillar ulcers. These lesions have also been bacteriologically studied by Bendix and Bickel.[86] Mollard[87] has reported a case with initial tonsillar involvement; death on the fifteenth day; necropsy showed numerous typical typhoidal ulcers of the intestines. According to Levy and Gaehtgens,[88] the portal of entry for the bacilli in some cases is doubtless the tonsils from which lymphatic dissemination occurs and eventually blood and intestinal infection. Kimla saw a unilateral tonsillar ulcer with *B. typhosus* in the necrotic tissues. Troullier[89] has mentioned specific ulcers of the soft palate, tongue, gums and pharynx, and in 220 typhoid patients he noted eighty-one with ulcers of the mouth and pharynx. In thirty-six of fifty-one cases, Manicatide[90] noted these ulcers from which the organism was isolated on Conradi-Drigalski media. Marquordt (cited by McCrea) reported having found ulcers of the pharynx, palate or tonsils in three or four cases at Ebstein's clinic. In a typhoid patient, Novotny[91] isolated the paratyphoid "B" bacillus from a palatal ulcer. While in the third Medical Clinic in Vienna he published statistics on laryngeal ulcers in typhoid fever. He describes them as being smooth, round or oval, sharply defined and shallow, and in the early stage with red margins. The bases are yellow or grayish yellow and without false membrane. On irritation they bleed

80. Cole, cited by McCrae: Osler's Modern Medicine, ii, 157.
81. Vincent: Recherches bacteriologiques sur l'infection mixte par le bacille typhique et le streptocoque, Bull. et mém. Soc. méd. d. hôp. de Paris, 1891, p. 561.
82. Picchi: La clin. méd., 1906, No. 37.
83. Vas: Pest. med.-chir. Presse, 1893, No. 36.
84. Besson: Rev. de med., 1897, No. 6.
85. Cappellari: Gazz. d. osp., 1899, No. 43.
86. Bendix and Bickel: Deutsch. med. Wchnschr., 1907, No. 23.
87. Mollard: Lyon méd., 1906, cvi, 798.
88. Levy and Gaehtgens: Arb. a. d. k. Gsndhtsamte, 1908, xxviii, 168.
89. Troullier: Gaz. d. hôp., 1908, No. 18.
90. Manicatide: Centralbl. f. Bakteriol. (Orig.), 1908, xlvi, 221.
91. Novotny: Wien. klin. Wchnschr., 1909, xxii, 779. (Literatur.)

slightly. Healing takes place without scars. The points of predilection are the anterior pillars and the soft palate. Gallois, Courcoux and Decobert[92] have demonstrated *B. typhosus* in nasal secretions of patients. Clifford and Moore[93] have recently noted a case of bilateral cancrum oris complicating typhoid fever in a patient 8 years old. Recovery. Keen has collected nine such cases from the literature and of these, five were fatal. In a series of necropsy records cited by McCrae in Osler's "Modern Medicine," four out of 2,544 typhoid cases showed esophageal ulcers. *B. typhosus* has been found in such ulcers, but most of them are probably due to simple pyogenic organisms. Two of these showed a diphtheroid esophageal membrane. Stricture is a rare sequel of the condition. Additional recent contributions to the literature on typhoidal lesions of the upper respiratory and alimentary tracts have been made by Blum,[94] Schmidt,[95] Lüdin[96] and Kirchgaesser.[97] A case of perforated typhoidal gastric ulcer has been reported. Chantemesse[98] and Guinard were apparently the first observers to call attention to the existence of typhoidal appendicitis. Posselt, McCrae, Stokes and Amick[99] have contributed to the literature. Posselt,[100] Mussat,[101] Mazeran,[102] Pfister,[103] von Czyhlarz[104] and Ortner[105] have noticed a complicating membranous enteritis. Thue's[42] case showed ulcers at the anus.

Bone.—Except for bone lesions developing during the course of typhoid fever these manifestations are not sufficiently unusual to justify their discussion. McCrae (Osler's Modern Medicine) cites a boy, 10 years of age, who during the course of the disease developed fluctuating masses on the frontal bone and on one rib. *B. typhosus* was not isolated from the pus.

Skin.—The more unusual cutaneous manifestations are herpes, urticaria, erythema, erysipelas, desquamation, gangrene, purpura, impetigo and striae atrophicae. McCrae has reported twenty cases of herpes in a

92. Gallois, Courcoux and Decobert: Rhino-pharyngite typoïdique à bacilles d'Eberth, Bull. et mém. Soc. méd. d. hôp., de Paris, Nov. 28, 1902.
93. Clifford and Moore: Jour. Am. Med. Assn., 1912, lviii, 1145.
94. Blum: Semaine méd., 1908, p. 37.
95. Schmidt: Ztschr. f. path. Anat., 1907, No. 15.
96. Lüdin: Ueber den diagnostischen Wert der typhösen Gaumenschwüre, Corr.-Bl. f. Schweizer Aerzte, 1910, xl, 751.
97. Kirchgaesser: München. med. Wchnschr., 1911, No. 23.
98. Chantemesse: Traité de méd.: Fièvre typhoïde.
99. Stokes and Amick: Typhoid Appendicitis without Other Intestinal Lesions, Bull. Johns Hopkins Hosp., 1905, xvi, 284.
100. Posselt: Ergebn. d. alleg. Path., 1912, i, 323.
101. Mussat: Bull. Soc. méd. de Reims, 1899, v, 354.
102. Mazeran: Jour. de med. de Paris, 1906, xviii, 112; Lyon méd., 1908, No. 30.
103. Pfister: Deutsch. med. Wchnschr., 1906, p. 1285.
104. von Czyhlarz: Arch. f. Verdauungskr., 1910, xvi, 576.
105. Ortner: Arch. f. Verdauungskr., 1910, xvi, 726.

series of 1,500 typhoid cases. Zinn[106] found them in ten of 190 cases. Among others, Krokiewicz and Wenzke have published case reports. Urticaria was observed by Miller[107] in two out of 150 cases. Murchison[108] was the first to call attention to the similarity of erythematous eruptions in typhoid fever and scarlet fever. Hutinel,[109] Parker[110] and Richon-Hanns[111] have reported cases. Some no doubt are combined infections, such as have been observed by Gayton,[112] Caiger,[113] Payne,[114] Griffiths,[115] Sequeira,[116] Cosgrove,[117] Coombs,[118] Gabe[119] and Tissot.[120] Erythema nodosum was noted by Osler.[121] Singer[122] has observed an acne-like eruption, Eggleston[123] a pustular and Higgins[124] and Osler[121] a pemphigoid eruption. The coexistence of measles and typhoid has been observed by Ringer,[125] Ringwood,[126] Chrystie,[127] Matiegka[128] and Da Costa. Rolleston[129] saw a 10-year-old boy, who, on the fourteenth day of typhoid fever, showed desquamation over the thorax, abdomen, thighs, heels and toes, some of the desquamated pieces being the size of a shilling. A case of exfoliative dermatitis has been reported by Diehl.[130] Some of the blebs were as large as a half dollar. Appiani[131] observed several cases of general desquamation and summarized the literature. Simmons,[132] Nicholls,[133] Hughes and Levy,[134] McCrae, Liebermeister, Uskins, Cursch-

106. Zinn: München. med. Wchnschr., 1895, xlii, 486.
107. Miller: Internat. Clin., iii, 60.
108. Murchison: Treatise on Continued Fevers in Great Britain, Ed. 2, 1873, p. 515.
109. Hutinel: Arch. gén. de méd., September, 1892.
110. Parker: Bull. Johns Hopkins Hosp., 1911, p. 79.
111. Richon-Hanns: Progrès méd., 1911, xxii, 387.
112. Gayton: Lancet, London, May 19, 1894.
113. Caiger: Lancet, London, 1894, i, 1137.
114. Payne: Lancet, London, 1894, p. 1264.
115. Griffiths: Lancet, London, 1893, ii, 1307.
116. Sequeira: Brit. Med. Jour., 1891, i, 586.
117. Cosgrove: Brit. Med. Jour., 1897, i, 29.
118. Coombs: Brit. Med. Jour., 1897, i.
119. Gabe: Brit. Med. Jour., 1894, p. 848.
120. Tissot: Progrès méd., 1909, p. 230.
121. Osler: Studies in Typhoid Fever, Johns Hopkins Hosp. Rep., p. 473.
122. Singer: Ueber Varietäten des Typhusexanthems und ihre Bedeutung, Wien. klin. Wchnschr., 1896, No. 15.
123. Eggleston: New York Med. Jour., 1910, p. 508.
124. Higgins: Bull. Johns Hopkins Hosp., 1910, xxi, 289.
125. Ringer: Lancet, London, June 30, 1889.
126. Ringwood: Lancet, London, July 7, 1889.
127. Chrystie: Univ. Med. Mag., December, 1888.
128. Matiegka: Prag. med. Wchnschr., Sept. 25, 1889.
129. Rolleston: Tr. Clin. Soc., London, 1890, xxiii, 84.
130. Diehl: Jour. Cutan. Dis., 1898, xvi, 222.
131. Appiani: Gazz. d. osp., 1907, No. 12.
132. Simmons: Delaware State Med. Jour., September, 1912.
133. Nicholls: Montreal Med. Jour., June, 1906.
134. Hughes and Levy: Arch. de méd. et de phar., August, 1892; quoted by Hare and Beardsley, Typhoid Fever and Exanthemata, Ed. 2, 1909, p. 179.

mann, Fiessinger and Weil[135] have written on hemorrhagic syndromes ("hemorrhagic putrid typhoid"—French) early and late in typhoid fever. Gangrene of the skin has been noted by Taupin,[136] Hare and Beardsley,[137] Jacobi[138] and Abt.[139] A Series of such cases has been described by McFarland[140] and Stahl.[141] Erysipelas was found by Liebermeister[142] in ten of 1,420 typhoid cases; in ten of 500 cases, by Griesinger.[143] Among others, Freudenberger,[144] Potain,[145] Thielmann,[146] Berthoud,[147] Martine,[148] Armiex,[149] and Hare and Beardsley[137] have reported cases of erysipelas. Wilks[150] was the first observer to describe patellar striae. Bradshaw,[151] Shepherd,[152] Troisier,[153] Northrup,[154] Fischer,[155] Köbner,[156] Duckworth,[157] Kaposi,[158] Gubler,[159] Bouchard,[160] Nonne,[161] Barie,[162] Langer,[163] and Bunch[164] have noted the condition. The most frequent site of these lesions is the patellar region and more rarely over the anterior surface of the lower third of the leg, over the abdomen and over the arms and fingers. Phillips[165] has summarized 1,230 typhoid cases from the Lakeside Hospital, Cleveland. Herpes were seen in 12 cases; urticaria in 21 cases; desquamation in 83 cases; erythema in 7 cases;

135. Fiessinger and Weil: Rev. de med., xxxii, No. 9.
136. Taupin: Jour. d. Con. méd.-chir., 1839, No. 7.
137. Hare and Beardsley: Typhoid Fever and Exanthemata, Ed. 2, 1909, pp. 177, 253.
138. Jacobi: Arch. Pediat., Dec. 15, 1899.
139. Abt: Jour. Am. Med. Assn., 1901, xxxvii, 445.
140. McFarland: Quoted by Hare and Beardsley, p. 179. (Note 134.)
141. Stahl: Quoted by Hare and Beardsley, p. 178. (Note 134.)
142. Liebermeister: Quoted by Hare and Beardsley, p. 253. (Note 134.)
143. Griesinger: Quoted by Curschmann in Nothnagel's Encyclopedia, Typhoid and Typhus Fevers, p. 325.
144. Freudenberger: Quoted by Hare and Beardsley, p. 258.
145. Potain: Quoted by Hare and Beardsley, p. 259.
146. Thielmann: Quoted by Hare and Beardsley, p. 257.
147. Berthoud: Quoted by Hare and Beardsley, p. 258.
148. Martine: Quoted by Hare and Beardsley.
149. Armiex: Quoted by Hare and Beardsley, p. 257.
150. Wilks: Guy's Hos. Rep., 1861, vii.
151. Bradshaw: Liverpool Med.-Chir. Jour., July, 1888.
152. Shepherd: Tr. Am. Dermat. Assn., 1890, xiv, 23.
153. Troisier: Bull. et mém. Soc. méd. d. hôp. de Paris, 1889, No. 12.
154. Northrup: Tr. Assn. Am. Phys., 1903.
155. Fischer: München. med. Wchnschr., 1904, p. 482.
156. Köbner: München, med. Wchnschr., 1904, p. 928.
157. Duckworth: Brit. Jour. Dermat., 1893, p. 357.
158. Kaposi: Diseases of the Skin, Hebra, iii, 262.
159. Gubler: Quoted by Bunch, Brit. Jour. Dermat., 1905, xvii.
160. Bouchard: Quoted by Bunch, Brit. Jour. Dermat., 1905, xvii.
161. Nonne: Quoted by Bunch, Brit. Jour. Dermat., 1905, xvii.
162. Barie: Semaine méd., 1888, p. 259.
163. Langer: Anzeig. d. k. k. Gesell. d. Aerzte., Wien., 1879, No. 28.
164. Bunch: Brit. Jour. Dermat., 1905, xvii.
165. Phillips: Skin Rashes in Typhoid Fever, Am. Jour. Med. Sc., Aug., 1910.

purpura in 6 cases; pemphigoid eruption in 4 cases; erysipelas in 2 cases; impetigo in 1 case; striae patellares, in 1 case. In the last mentioned there were 42 transverse striations over the patellae and lower third of the legs.

DUAL INFECTIONS

The coexistence of miliary tuberculosis and typhoid fever was observed by Meunier[166] in an 8-year-old boy in whom a generalized miliary tuberculosis was present without evident typhoidal lesions; nevertheless *B. typhosus*, as well as *B. tuberculosis*, was isolated from the spleen, pleural fluid and lungs. Griffon[18] has reported a case of mixed infection with a streptococcus isolated from the bronchial pus, spleen, gall-bladder and bone-marrow together with *B. typhosus* from these organs. A case of endocarditis was reported by Nattan-Larrier,[48] who isolated a streptococcus and *B. typhosus* from the heart's blood and spleen, and the former from the miliary abscesses in the kidneys. Vincent[167] isolated the same types of organisms from the spleen, liver, kidneys and heart's blood in a case without intestinal lesions. Typhoid fever has coexisted with various other infections, such as diphtheria, scarlet fever (Fournier), measles, malaria, small-pox, chicken-pox, whooping-cough, etc.

INFANCY AND CHILDHOOD

Typhoid fever in early life, according to some writers, is likely to assume a septicemic form and to present no typical intestinal lesions. The disease is certainly more common at this period of life than was once supposed. There appears to be a tendency toward localization of lesions in the lungs and central nervous system. Griffith and Ostheimer[168] have reported on twelve congenital cases. Sacquépée and Chevrel[169] noted two cases in patients 3 and 4 years old, without involvement of the bowel, with agglutinations 1:200 and 1:300 and with *B. typhosus* from the heart's blood. A 16-months-old child with suppuration of both parotids was observed by Goldberger.[170] Halbron and Nandrot[171] have reported a case of a 5-year-old boy with ambulant typhoid and perforation. Barrett[172] observed a 2-year-old child with intestinal hemorrhage and remittent fever, but no roseola nor splenic enlargement. There were symptoms of meningitis. Additional cases of typhoidal septicemia without intestinal involvement have been reported by Cheadle, Bryant, Guiz-

166. Meunier: Bull. et mém. Soc. méd. d. hôp. de Paris, 1897, 476; Semaine méd., 1897, p. 121.
167. Vincent: Ann. de l'Inst. Pasteur, 1893, vii, 141.
168. Griffith and Ostheimer: Quoted by McCrae, Osler's Modern Medicine, ii, 176.
169. Sacquépée and Chevrel: Progrès méd., 1909, p. 73.
170. Goldberger: Aerztl. Ztrl.-Anz. Wien., 1896, viii, 209.
171. Halbron and Nandrot: Tribune méd., Paris, Oct. 14, 1905.
172. Barrett: Med. Rec., New York, lxxx, No. 2145.

zetti, Opie and Bassett, Lazarus-Barlow,[173] Lucksch,[174] Ribadeau-Dumas and Boyé,[175] and Schottmüller.[176]

TRAUMATISM

This has been suggested as an important predisposing factor in typhoidal suppurations. Seiler[177] has presented a dissertation on post-traumatic typhoidal peritonitis and Sennert,[178] on liver abscess as a sequel of trauma. The case of Sergent and Bernard[179] developed a typhoidal meningitis, according to the observers, after a bullet wound in the head. Gurd and Nelles[71] reported the case of cerebral abscess presumably developing in consequence of a head injury. The abscess was said to be of typhoidal character. Barjon and Lesieur[180] have presented a case of "arthrotyphus" succeeding "rheumatism," when trauma possibly played some part.

AGGLUTINATION REACTIONS

At times a moderately strong typhoidal agglutinating blood-serum is observed when the individual obviously presents no clinical evidence of typhoid fever. One of five possibilities may exist: (1) an infection with some other organism of the typhoid-colon-dysentery group; (2) a typhoidal infection of "extra-intestinal type"; (3) a recent typhoidal infection; (4) a recent prophylactic vaccination; (5) "typhoid carrier." Positive serum agglutinations with typhoid bacilli have been reported in miliary tuberculosis, pneumonia, sepsis, etc., but a previously existing typhoidal infection probably accounts for most, if not all, of these. Symmers and Wilson[181] have reported a case of epidemic cerebrospinal meningitis having a Widal positive 1:200. There was no previous history of typhoid fever. Necropsy showed no intestinal involvement and bacteriological examination of spleen, mesenteric nodes and urine was negative. Meningococci in pure culture isolated from meninges. Stelker[182] reported another epidemic meningitis case with a Widal positive 1:100. Becker and Ruhland[183] have made further reports.

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173. Lazarus-Barlow: Brit. Med. Jour., 1901, p. 792.
174. Lucksch: Centralbl. f. Bakteriol. (Orig.), 1903, xxxiv, 113.
175. Ribadeau-Dumas and Boyé: Arch. d. méd. d. enf., 1909, xii, 584; Jahrb. f. Kinderh., 1910, p. 105.
176. Schottmüller: München. med. Wchnschr., 1911, p. 469.
177. Seiler: Posttraumatische Peritonitis typhosa bei bestehender typhöser Cholezystitis, Inaug.-Dissert., Berlin, Nov., 1910.
178. Sennert: Inaug.-Dissert., Halle, July, 1906.
179. Sergent and Bernard: Bull. et mém. Soc. méd. d. hôp. de Paris, 1901, p. 57.
180. Barjon and Lesieur: Province méd., Oct. 27, 1900; Jour. d. Phys. et Path. gén., 1901, p. 150.
181. Symmers and Wilson: Brit. Med. Jour., 1907, p. 713.
182. Stelker: Russk. Vrach., 1907, No. 8.
183. Becker and Ruhland: Jour. Am. Med. Assn., 1909, lii, 13.

THROMBOPHLEBITIS

Though not an unusual lesion of typhoid fever, thrombophlebitis bears mention in this place. One of the most recent and exhaustive summaries of this condition has been published by Connor[184] in a study of eighty-two cases. He states that the condition is more common than is supposed (10 to 15 per cent. of all cases of typhoid fever), that it is gradual in development and that it is more extensive than the symptoms would indicate. He believes that most pulmonary and pleural complications late in typhoid fever are due to embolism of the pulmonary artery, that obscure, late, recurring chills are regularly associated with venous thrombosis, and that "tender toes" in the majority of cases are caused by thrombophlebitis.

Lesions of the intestines, mesenteric nodes and spleen were absent in those cases reported by Lazarus-Barlow, Pick,[185] Picchi, Barjon and Lesieur and Vanzetti. Unusual splenic enlargement was noted by Nicholls and Keenan,[186] Bozzolo,[187] Karlinski,[21] Doglietti,[16] Guizzetti[23] and Blumenthal.[17] An unusually small spleen (one-half normal) was reported by Roscoe.[188] Monroe and Campbell's[19] case showed perisplenic abscess; Picchi's and Blumenthal's cases, renal infarcts. In the cases without intestinal lesions, "pea-soup stools" were observed by Hodenpyl,[189] Blumenthal, Jores[190] and Posselt. In the same class of cases, *B. typhosus* was isolated from the stools by Hodenpyl, Pick, Bobbio, Gennari,[191] Farcy,[192] Etienne and Thiry. This organism was isolated from the mesenteric nodes by Lartigau (also *B. coli*), Bryant, Nicholls and Keenan, Banti,[193] Chiari[194] and Vestenrik.[195]

A review of the literature reveals a large number of cases classified as atypically typhoid, but in many of these the diagnosis of lesions was not established by bacteriological examination. Many cases have been published as primary typhoidal gall-bladder infections in which it seems probable that a previously existing infection left the patients as "carriers." Nevertheless, many writers, among whom are McCrae, Phillips, Luksch, Chiari, Brion, Keyser and Posselt have laid emphasis on the

184. Connor: THE ARCHIVES INT. MED., 1912, x, 534.
185. Pick: Wien. klin. Wchnschr., 1897, p. 82.
186. Nicholls and Keenan: Montreal Med. Jour., 1898, xxvii, 9.
187. Bozzolo: Tenth Internat. Med. Congress, Berlin, 1890, ii, 188; Wien. med. Wchnschr., 1890, p. 226.
188. Roscoe: Lancet, London, Oct. 16, 1909.
189. Hodenpyl: Brit. Med. Jour., 1897, p. 1850.
190. Jores: München. med. Wchnschr., 1911, p. 1247.
191. Gennari: Gazz. d. osp., 1907.
192. Farcy: Thèse de Paris, 1909, No. 267.
193. Banti: Riforma med., 1894, x, 674.
194. Chiari: Ztschr. f. Heilk., Prague, 1897, xviii, 471.
195. Vestenrik: Soc. d. microb. de Saint Petersburg, 1904.

fact that typhoid infection without intestinal lesions is a very rare condition. In twenty years at the Institute of Pathological Anatomy at Innsbruck, von Hibler failed to note a case. In 1899, Howard[9] collected from the literature 164 cases of typhoidal infection (including mixed infection) without intestinal localization. During the same year McPhedran[196] published a summary of twenty cases. In 1912, in Lubarsch and Ostertag's "Ergebnisse der allgemeinen Pathologie," Posselt presented an admirable review of the literature, and states that only 63 cases fulfill the requirements of accurate bacteriological examinations.

Primary typhoidal septicemia	28
(Mixed infection, including tuberculosis)	7
Primary typhoidal meningitis	3
Primary typhoidal affections of the lungs	2
Primary typhoidal affections of the pleurae	1
Primary typhoidal affections of the spleen	3
Primary typhoidal affections of the kidneys	2
Primary typhoidal affections of the joints	1
Primary typhoidal affections of the liver and bile ducts	16
	63

On reviewing the reports it is quite evident to us that the literature contains many incomplete and inaccurate observations, but the above table evidently does not include a number of authentic reports.

As to the nomenclature, the German and French writers have made much use of the terms, meningo-typhoid ("meningotyphus"), pneumotyphoid ("pneumotyphus"), etc. It has been suggested that the terms, as indicated in the above table, should be employed. However, the foreign terms have been employed with broader significance so as to imply not necessarily a primary lesion without intestinal involvement, but to emphasize in general a dominant or unusual lesion in a case otherwise presenting the classical evidences of typhoid fever.

SUMMARY OF CASES

The following represents a summary of cases at the Southern Pacific Hospital, San Francisco, and others seen in private practice and consultation, illustrating atypical conditions and complications. Among 149 patients treated at the new hospital since its opening in September, 1909, there have been 11 deaths—7.3 per cent.; with meningitis, chronic nephritis and purulent appendicitis, each 1 case; intestinal hemorrhage, 2 cases; perforation and possibly embolism, each 3 cases. There were 3 paratyphoid cases. Relapses developed in 9 cases, of which one appeared as late as four weeks after leaving the hospital. The longest febrile period of relapse was thirty days and the shortest, nine days. One patient devel-

196. McPhedran: Can. Jour. of Med. and Surg., Toronto, 1899, vi, 251; Philadelphia Med. Jour., 1900, i, 543.

oped a second attack of typhoid fever after a six-year interval. The earliest intestinal hemorrhage occurred on the third day. Two cases were fatal and of 11 others, 4 were severe and 7 were mild. Pleurisy with effusion (organism?), meningitis and pneumonia (*B. typhosus*), neuritis in leg, neuritis in shoulder, periostitis of tenth rib and perforating duodenal ulcer were each noted in one case. The ulcer patient was operated on on the twenty-ninth day, but the lesion was not determined as typhoidal. Two patients presented an initial appendicitis, the operation being followed by the development of typhoid fever. Another patient during the course of typhoid infection developed the symptoms of perforation; operation was performed and a ruptured appendix was disclosed. Phlebitis of the leg developed in 7 cases, and of these there were 4 in the second week, 2 in the fifth week and 1 in the third week after discharge. Thrombosis or embolism was suspected in the lungs in 4 cases and in the mesenteric veins in 3 cases. These occurred from the sixth to the thirty-fifth days, and were not severe, except in 2 cases of pulmonary embolism. One patient died promptly, and the other, occurring on the thirtieth day, resulted in gangrene from which the patient was convalescent on the one hundred and ninety-first day. Chills and fever were noted in 13 cases of which phlebitis of the leg was the etiological factor in 3. Malaria may have been a factor in another case. Chills occurred during the first week in 4 cases, second week in 2 cases, third week in 4 cases, fourth week in 2 cases and sixth week in 1 case.

In California and Nevada, 47 cities and towns furnished typhoid cases. San Francisco, 17; Sacramento, 14; Oakland and Alameda, 13; Bakersfield, 5; Sparks (Nevada), 25.

Additional cases are quoted in brief to illustrate certain of the complications, two cases of hemorrhagic form being especially uncommon.

Typhoidal Cholecystitis.—F. F., male, aged 40 years, had an afebrile period of one week following typhoid fever. Then developed chilly sensations, epigastric pain, muscular spasm, tenderness in right hypochondrium, slight jaundice, nausea and vomiting. Leukocytes, 6,000; neutrophils, 50 per cent. Within a few days distinct tumor of the gall-bladder elicited, but this had subsided at the end of a week. Highest temperature 103 F. Duration of attack eighteen days. Three years later there had been no further gall-bladder symptoms.

Thrombosis of Mesenteric Vessels.—V. J. D. C., male, aged 40 years, was seen in the fifth week of typhoid fever. His general condition had been excellent throughout the course of the disease. During the last ten days there had been successive crops of "rose spots" over the abdomen and back. On examination the abdomen was found to be tympanitic and there was especial distention in the right lower quadrant. Tenderness had been present in this region for some time, according to the previous examiners. There was no dulness in the flanks. Spleen reached to the costal margin. Diagnosis.— Probable thrombosis of mesenteric vessels though condition of relapse was considered. Perforation and complicating appendicitis were eliminated.

Venous Thrombosis.—R. E. W., male, aged 20 years. A probable relapse was considered. The usual course of typhoid infection was succeeded by an afebrile

period of seven days. Rise of temperature then developed, lasting four days, during which time he was seen by one of us (P. K. B.). Blood count indicated a late typhoidal condition and no pyogenic complication. A probable relapse was considered. Temperature fell and remained normal for seven days, throughout which time he had a profuse diarrhea, most severe the last two days. Then a sudden rise of temperature to 104 F. appeared, followed by collapse (96 F.). The pupils were widely dilated, extremities cold and clammy, and there were profuse sweats, very feeble low tension pulse of 80 to 90, respirations 20, no evidence of perforation. Strychnin and salt solution were administered with good results. During the next five days he had six similar collapses, often sudden in onset. Pulse did not become rapid, but extremely slow and feeble. Respiration shallow. No unconsciousness. Intravenous or subcutaneous salt solution injections were most effectual. No especial abdominal tenderness. Diagnosis.—Probable thrombosis.

Hemorrhagic Typhoid.—(1) C. B. E., male, aged 21 years. "Rose spots" appeared on the sixth day and positive Widal on the seventh. Several intestinal hemorrhages on the ninth day with hematuria and generalized purpura. On the third day bleeding from nose and gums. Death on the twenty-eighth day.

(2) J. M. G., male, aged 36 years. Seen in the third week of typhoid fever. Widal positive on the tenth day. Usual course during first two weeks. On the sixteenth day a large number of small subcutaneous hemorrhages over back from transverse process of scapula to level of sacrum. Small crop covered upper part of buttocks. During the third week patient had hemorrhage from nose, stomach and intestines. Pulse 104 to 120. Very restless. Calcium salts administered per rectum in small doses. Died the following morning.

To the subject in hand no words are more fitting than those of Murchison relative to typhoid fever: "There is no disease, in fact, which exhibits a more protean character, from predominance of certain symptoms, and from the presence of complications."

THE ABSORPTION OF PROTEIN WITHOUT DIGESTIO *

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The purpose of the experiments reported in this paper is to dete ine whether it is possible for a protein to be absorbed through the epit ium of the gastro-intestinal tract and appear in an unaltered form the circulating blood. This question is not a new one in the physio y of digestion. It has been studied by many workers who have empl ' a variety of experimental methods. Most of the experiments now q' ed in the literature were made before the biological specificity of protein was recognized. It is obviously impossible to distinguish sharply between closely allied animal proteins by purely chemical reactions, such as the measurement of the content of nitrogen, phosphorus, sulphur, or by means of the salting-out methods. The newer biological methods, such as the precipitin and anaphylactic reactions, have a high degree of biological specificity, and enable one to distinguish sharply between proteins so closely related as the blood-serum proteins of the horse, beef and sheep, and enable one to distinguish each protein in the presence of others. It is now possible, therefore, by means of these reactions to trace a protein through the intestinal tract into the circulation, to identify it there as an unchanged protein, to determine the length of time it remains in the circulation, and after its excretion by the kidney to identify it in the urine. Because the anaphylactic reaction is so sensitive, and because a positive reaction can be so sharply distinguished from a doubtful or negative reaction, it has been used almost exclusively in the experiments which are herein reported.

When the protein-splitting action of the digestive ferments was first discovered it was thought that the primary cleavage products, proteoses and peptones, were the form in which protein entered the circulation. These substances are soluble and diffusible, and because they may pass through parchment membrane they were believed to be absorbed in this form into the circulation. Further experiments showed, however, that these substances when introduced directly into the blood were highly toxic,[1] and examination of the blood-serum after a heavy protein meal did not show an increase in the proteoses.[2] In fact, recent experiments

* From the Department of Experimental Therapeutics, Cornell University Medical School.
* Submitted for publication July 8, 1913.
1. Underhill: Am. Jour. Physiol., 1903, ix, 345.
2. Howell: Am. Jour. Physiol., 1906, xvii, 273.

show "proteoses or peptones are not found in the blood, even in the portal blood, collected during the period of maximal absorption from the intestines."[2]

It must be remembered that the blood-serum proteins have a biological specificity; their character does not appreciably change with the character of the diet. Regardless of whether the protein in the food is vegetable or animal in character, the blood-serum proteins have a constant composition. The more recent investigations of the cleavage action of the digestive enzymes indicate that the splitting normally proceeds much farther than was originally believed, and results in the formation of a variety of amino-acids from which protein may be synthesized either by the absorbing epithelium or by other tissues, possibly the liver, after their entrance into the circulation. In fact, there is conclusive evidence that amino-acids are constantly present in the circulating blood.[3] It is believed, therefore, by the majority of physiologists at present that the protein taken in the food is reduced by the process of digestion to the small constituent amino-acids, the so-called "bausteine," which are absorbed as such and resynthesized into protein, either by the intestinal epithelium before reaching the circulation, or by other tissues after the absorption is completed.[3] However, further recent experiments indicate that not all of the amino-acids so formed are used at once for protein synthesis in the manner described.[4] It is well known that the majority of animals take more protein in the food than is required to replace the waste in the tissues. Nitrogen equilibrium may be maintained at a much lower level than the protein intake ordinarily provides. It is believed that a considerable proportion of the amino-acids absorbed after a protein meal are broken down still further, and quickly eliminated, giving rise to the increased nitrogen output which promptly follows nitrogen consumption. In this theory there is no place for the assumption that soluble protein may be absorbed directly without this preliminary cleavage. It must not be overlooked, however, in the light of recent knowledge, that comparatively insignificant amounts of foreign protein may give rise to disturbing and serious manifestations if it gains access to the circulation in an unaltered condition. The amount of nitrogen which, in the form of an alien protein, may cause toxic reactions menacing the life of the animal is so small as to be beyond discovery by the methods commonly followed in measuring the energy exchange.

It was formerly believed that a parenterally introduced protein could not be utilized in the processes of nutrition either as a source of nitrogen or of energy. It was supposed that such protein was immediately

3. Hammersten-Mandel Text-Book, 1909, p. 412. Abderhalden Text-Book, 1908, pp. 119 and 532.

4. Folin, Otto: Am. Jour. Physiol., 1905, xiii, 117.

excreted by the kidney. New light has been turned recently on this problem by a number of investigators who have demonstrated that the older ideas are incorrect, and that a considerable portion of such protein, the percentage varying with the character of the protein introduced, may be utilized.[6, 7] One may not conclude, therefore, that because no gross quantity of foreign protein appears in the urine after it has been taken as food that none of it has been absorbed as unchanged protein directly into the circulation.

The evidence now quoted in the literature to substantiate the claim that protein may be absorbed without digestion is with few exceptions based on two lines of argument, neither of which gives a positive demonstration that the same identical protein which is introduced into the intestine finally appears in the circulation.

1. The first of these arguments is based on the fact that parenterally introduced protein is not all excreted as such, but is available in some degree for the nutritive requirements of the organism.

2. The second is based on the fact that if certain proteins be introduced into a loop of the intestine or into the colon by rectum and allowed to remain there for varying lengths of time, not all of such protein can be recovered by thoroughly washing out the experimental loop.

The first method of reasoning was followed by Munk and Lewandowsky,[6] who injected casein, egg albumin, acid and alkali albuminates, nucleoproteins and gelatin directly into the circulation and found that not all of the protein so introduced was excreted in the urine. As one conclusion of these experiments they claim to be the first investigators to demonstrate that protein enters unchanged from the intestinal canal directly into the circulating blood. Such a conclusion from such evidence is obviously pure assumption. Numerous other experiments have confirmed their findings with respect to the partial utilization of parenterally introduced protein, but, obviously, such evidence does not prove that protein passes through gastro-intestinal epithelium unaltered.

The second method of experimentation has been employed by many investigators.[7] The evidence which they offer proves beyond doubt that native protein may disappear from a section of the intestine even though digestive enzymes cannot be demonstrated to have any part in the process. It is assumed that because proteins disappear and because no protein-

6. Munk and Lewandowsky: Arch. f. Anat. u. Physiol., Suppl. Vol., 1899, p. 73; Cramer: Brit. Jour. Physiol., 1909, xxxvii, 146; Oppenheimer: Hofmeister's Beitr. z. Chem. Phys. u. Path., 1904, iv, 263; Heilner: Ztschr. f. Biol., 1907, l, 26.

7. Friedländer: Ztschr. f. Biol., 1897, xxxiii, 264; Czerney and Latschenberger, Virchows Arch. f. path. Anat, 1875, lix, 161; Eichherst: Pflügers Arch. f. d. ges. Physiol., 1873, iv, 570; Voit and Bauer: Ztschr. f. Biol., 1871, v, 536; Mendel and Rockwood: Am. Jour. Physiol., 1904, xii, 336.

splitting enzymes can be demonstrated in the loop, that the protein has been absorbed unchanged. This is an obvious conclusion, but one not satisfactorily demonstrated.

Probably the first attempt to make a direct demonstration that unaltered alien protein may appear in the blood after its introduction into the gastro-intestinal tract was that of Ascoli and Vigno,[8] who employed the precipitin reaction as a method of identification. These men experimented entirely with dogs. They collected lymph from the thoracic duct and blood from the jugular vein after egg white and coagulated fowl meat had been introduced into the stomach through a tube. They found that the serum from such animals did not give uniformly constant precipitin reactions with the immune serum; but their reactions were sufficiently constant and sharp to force them to the conclusion that the foreign protein may be absorbed through the stomach either in its native condition or so little modified as not to interfere with its biological reactions. These experiments have been widely quoted in support of the view that undigested protein may pass through the intestinal epithelium unchanged, but they leave the matter still in doubt as to whether the native protein itself or one of its primary cleavage products was the substance actually identified in the blood.

The accuracy and reliability of the experiments herein reported depend on the anaphylactic reaction as a suitable method for identifying the protein. The studies of Wells[9] and Wells and Osborne[10] afford particularly convincing evidence of the suitability of this reaction for this purpose. In a recent paper they have summarized the information as to the specificity of the anaphylactic reaction, and Wells has determined to what extent the processes of digestion so alter a protein as to destroy its specific character as an antigen. It does not seem necessary, in view of the excellent summary which is given in their paper,[10] to review this matter in detail. The earlier conclusions of Rosenau and Anderson[11] in regard to this matter have not been materially modified by recent work. They summarize their conclusions with respect to the specificity of the anaphylactic reaction as follows:

> The anaphylactic reaction in the guinea-pig, therefore, seems to be specific in the sense that the precipitins are specific. That is, there is a group reaction in the proteins of allied species, but no reaction between the proteins of widely different species or between proteins of widely different origin.

The testimony of all investigators is agreed that, with few exceptions, notably the protein from the crystalline lens, there is a species specificity

8. Ascoli and Vigano: Ztschr. f. physiol. Chem., 1904, xxxix, 283.
9. Wells, H. Gideon: Jour. Infect. Dis., 1909, vi, 506; 1908, v, 449.
10. Wells and Osborne: Jour. Infect. Dis., 1911, viii, 66.
11. Rosenau and Anderson: Jour. Infect. Dis., 1908, iv, 552.

to protein which may be sharply identified by means of the anaphylactic reaction. Wells[12] has carried the matter somewhat further in particular cases, and has demonstrated that within a given species there is a specificity which enables one sharply to distinguish proteins. For instance, in a recent work he has demonstrated that:

> In hen egg-white there are at least four antigens (three in the coagulable protein and one non-coagulable) which can be distinguished by the anaphylaxis reaction, and therefore are biologically distinct from one another, although coming from a single secretion. At least one other protein of the egg, the ovovitellin, can be differentiated from the other three egg antigens, so that we have here demonstrated five antigens in the egg which are biologically distinct in spite of a common origin. These must be looked on as examples of chemical specificity independent of species specificity. The antigens distinguished by the anaphylaxis reaction seem to correspond to the proteins which have been distinguished by chemical means.

Besides our own experiments, those of many others confirm the principle originally discovered by Rosenau and Anderson that guinea-pigs may be sensitized to a number of proteins at the same time and react to each separately. Rosenau and Anderson's observations are as follows:

> A guinea-pig sensitized with milk, egg-white, and horse serum, either together or separately, will react with each of the three fluids given in the series. The blood of such a triply sensitized animal when injected into other animals will likewise render them passively sensitive to all three.[13]

It must be evident from this work that no method compares with anaphylaxis as a means of sharply distinguishing closely allied proteins. For the purpose of the experiments which form the basis of this paper, it is important to note that the digestion of protein seriously interferes with its giving the anaphylactic reaction. The most conclusive evidence on this point is afforded by the experiments of Wells,[14] who found that traces of coagulable protein remained after sixteen months' digestion with trypsin and that such almost completely digested protein would still sensitize to the homologous antigen, but only when very large doses were given, and even then the sensitization was so mild as not to give a fatal result. He states that

> Pepsin-HCl digestion of egg albumin destroys its sensitizing and intoxicating properties very slowly, the former existing to a slight degree even after coagulable protein cannot be longer demonstrated. Conversion of egg albumin into acid albumin somewhat impairs, but by no means destroys, its powers to sensitize guinea pigs to egg albumin and to intoxicate pigs that have been sensitized with egg albumin.

He found, also, that as determined by the anaphylactic reaction, serum is much more resistant to tryptic digestion than egg albumin.

12. Wells: Jour. Infect. Dis., 1911, ix, 147.
13. Rosenau and Anderson: Jour. Infect. Dis., 1908, iv, 552.
14. Wells: Jour. Infect. Dis., 1909, vi, 506.

The formation of acid albumin is, however, probably not accompanied by any considerable change of the molecule, and although such a process may be considered to be the first step to protein digestion, it is not to be compared with the cleavage action of the enzymes which break up the protein molecule into the various proteoses and amino-acids. These latter substances are to be considered as the true products of digestion in the gastro-intestinal tract, and Wells' experiments demonstrate that these substances

have no power to sensitize or intoxicate guinea-pigs, whether used in conjunction with themselves or with undigested egg-white. To quote further:

These experiments indicate that proteins cannot be decomposed much, if any, beyond the coagulable form without losing their anaphylactic properties. For the anaphylaxis reaction we must have intact protein molecules in soluble form. Possibly there exists a stage intermediate between the entire protein molecule and the ordinary proto- and duetero-proteoses, with which anaphylaxis can be produced, for coagulated proteins digested with either pepsin or trypsin show at certain stages a slight power to sensitize animals to egg albumin, but the power is very slight.

In the course of the experiments which are detailed below, the absorption of a variety of proteins has been tested—egg-white, milk, beef serum, horse serum and edestin. They have been introduced into the intestinal tract in some instances by means of the stomach-tube, or by hypodermic injection through the intestinal wall; in other cases into the stomach which had been ligated at both cardiac and pyloric ends or into ligated loops of the intestine, and in still others into Thiry-Vella fistulae, which were made in different portions of the intestine. It will be seen that both animal and vegetable proteins have been tested in normal conditions of absorption and in conditions in which some degree of impairment of digestive function may be presumed to exist.

A preliminary paper[15] has already been published giving the details of some of the earlier experiments, and from this paper such quotations will be made as have important bearing to the later work. The first point determined in the earlier paper was the question as to whether a foreign protein, egg albumin, could be injected directly into the circulation of a dog and remain there for several hours in such form that its presence could be detected by means of the anaphylactic reaction. The details of one of these experiments is quoted as follows:

A healthy dog was placed in a cage for a few days for observation and to obtain samples of urine. The animal was found to be well in all respects and the urine free from albumin. Under morphin and cocain anesthesia the jugular vein was aspirated and 100 c.c. of blood drawn to obtain normal serum. Following this procedure 20 c.c. of an egg albumin solution prepared as follows was injected into the vein: The whites of fresh eggs were thoroughly broken up and diluted with an equal volume of salt solution. The solution filtered through paper was ready for use. Fifteen minutes after the albumin was injected 20 c.c.

15. Van Alstyne and Grant: Jour. Med. Research, 1911, xxv, 399.

of blood was withdrawn, and again at four hours, forty-eight hours, and seventy-two hours after the injection a further quantity was withdrawn. The serum from this blood was allowed to separate and kept for sensitizing purposes. The urine was collected daily and examined for albumin, and a portion of it kept for sensitizing purposes.

Guinea-pigs were sensitized with the serum and urine obtained as outlined above, the sensitizing dose varying from one-tenth cubic centimeter for the first twenty-four hours to five-tenths cubic centimeters for the seventy-two-hour period. One cubic centimeter of the urine was used for the same purpose. The sensitizing dose of serum was given subcutaneously and, after an appropriate period, in no case less than ten days, an intoxicating dose of the egg albumin solution, 2.5 or 3 c.c., was given intraperitoneally.

TABLE 1.—ANAPHYLACTIC REACTION IN GUINEA-PIGS PRODUCED BY BLOOD AND URINARY PROTEINS FROM DOGS WITH THIRY-VELLA FISTULAE

No. of Dog	No. of Guinea-Pig	Fistula	Substance Used for Sensitizing Dose	Toxic Dose	Results
675	273 *	Middle of small intestine	Serum drawn before albumin in fistula	Egg albumin	No symptoms
675	300	Middle of small intestine.	Serum drawn one hour thirty mins. after albumin in fistula	Egg albumin	Severe symptoms. Recovered
646	333	Eight inches below duodeno jejunal fossa.	Serum drawn three hours after albumin in fistula	Egg albumin	Severe symptoms. Recovered
667	612	Eight inches from cecum	Serum drawn one hour forty min. after introducing albumin in fistula	Egg albumin	Dead in forty-five minutes
...	354	Eight inches from cecum	*Albumin from urine	Egg albumin	Marked symptoms. Recovered
...	327	Eight inches below duodeno jejunal fossa	Urine from twelve to twenty-four hours after albumin in fistula	Egg albumin	Severe symptoms. Recovered

* This pig was sensitized by giving him the protein obtained by one-half saturation of the urine with ammonium sulphate.

The results of this line of experimentation show that the serum of the dog to which the albumin was given intravenously was capable of sensitizing guinea-pigs to the subsequent dose of egg albumin. The egg albumin, therefore, was not immediately excreted or fixed in the tissues, but remained in the serum for at least three days in such concentration that five-tenths cubic centimeters of serum would sensitize a pig to a slight degree.

The egg albumin must have been excreted in the urine, for qualitative tests made of the first twenty-four-hour urine showed a small amount of albumin, and a pig sensitized with 1 c.c. of it gave a severe anaphylactic reaction.

All of the experiments in which dogs with a Thiry-Vella fistula were used have been published in a preliminary paper and the essential facts in these experiments will be quoted. The fistulae were made in three

different positions of the intestine: (1) Just below the duodeno-jejunal junction; (2) about the middle of the ileum, and (3) low down in the ileum. In the accompanying table (Table 1), which is condensed from the published preliminary paper, are given the experimental details and results obtained with those animals.

It does not seem possible to avoid the conclusion that the egg albumin had passed from the fistula into the circulation without alteration. These fistulae were made at a point in the intestine where the possibility of the formation of acid albumin is ruled out. It is not contended that these intestinal loops contained no digestive ferments or that a portion of the protein may not have been digested before absorption. The evidence is positive, however, that a portion of it entered the circulation without alteration and was excreted by the kidney in such form as to be precipitated by half saturation with ammonium sulphate. The amount of protein obtained from the urine was so small as to warrant the belief that a portion of the absorbed protein was utilized in the body. These experiments do not indicate how large a portion of the protein was absorbed without digestion, nor can it be assumed that absorption from a Thiry-Vella fistula is exactly identical with the absorption of protein from the same region of the intact intestine.

Since these experiments were positive, it seemed advisable to continue the investigation with somewhat different methods and with a variety of proteins. The question arose as to whether the same positive results would be obtained if the egg albumin should be introduced into the stomach by means of a tube. It can scarcely be assumed that such a method of introduction would in any measurable way interfere with the normal digestive processes. Accordingly, a dog was prepared in the usual fashion, blood was aspirated from the jugular vein before egg-white was introduced into the stomach, and preserved for further use. The whites of five eggs were beaten up with an equal quantity of salt solution and introduced into the stomach directly through a tube. Table 2 gives the experimental details.

The tabulated results indicate that either a small amount of egg albumin passed through the stomach walls without digestion or that some of it may have been absorbed as an acid albumin. Wells has shown that acid albumin sensitizes in slight degree to the unaltered protein. At any rate, it is fair to conclude that under these conditions only an exceedingly small portion of the ingested protein passed through unaltered.[14]

In the next experiment the technic was modified in that a ligature was placed around both the cardiac and pyloric ends of the stomach to insure the retention of the albumin in the organ. The experimental details are given in Table 3.

TABLE 2.—Experiments in Anaphylaxis in Guinea-Pigs Sensitized with Blood and Urinary Proteins from Dogs with Thiry-Vella Fistulae Fed Egg Albumin Per Stomach

No. of Dog	No. of Guinea-Pig	Sensitizing Dose	Period of Incubation Days	Toxic Dose	Results
520	372	Eight min. dog serum before albumin introduced	21	(a) 3 c.c. egg albumin intraperitoneally. (b) 2 c.c. dog serum two days later	(a) No symptoms (b) Symptoms +
...	373	Eight min. dog serum one hour after albumin in stomach	21	(a) 2 c.c. egg albumin intraperitoneally. (b) 3 c.c. normal dog serum intraperitoneally two days.	(a) Mild symptoms (b) Symptoms +
...	374	Eight min. dog serum two hours after albumin in stomach	21	(a) 3 c.c. egg albumin intraperitoneally. (b) 3 c.c. normal dog serum intraperitoneally two days later	(a) Mild symptoms (b) Symptoms +
...	375	Eight min. dog serum three hours after albumin in stomach	21	(a) 3 c.c. egg albumin intraperitoneally. (b) 3 c.c. normal dog serum intraperitoneally two days later	(a) Mild symptoms (b) Dead two days later
...	376	Eight min. dog serum five hours after albumin in stomach	21	3 c.c. egg albumin intraperitoneally.	Mild symptoms
...	377	Eight min. dog serum twenty-four hours after alb. in. stom.	21	3 c.c. egg albumin intraperitoneally.	No symptoms
...	558	Albumin from urine first twenty-four-hour period (dialysis)	21	3 c.c. egg albumin intraperitoneally.	No symptoms
...	516	Five c.c. dog serum drawn twenty-three days after albumin in stomach	21	3 c.c. egg albumin intraperitoneally.	No symptoms
...	518	Five c.c. dog serum drawn twenty-three days after albumin in stomach	21	3 c.c. egg albumin intraperitoneally.	No symptoms
...	515	One c.c. each one, two, three, five-hour bleedings plus 1 c.c. fresh normal dog serum.	21	1 c.c. egg albumin intravenously	Mild symptoms

Note 1.—In view of the fact that guinea-pigs often exhibit toxic symptoms which resemble some of the characteristic symptoms of anaphylaxis and that any guinea-pig may be restless and shake itself as the result of the handling incident to the intravenous injection of the toxic dose, I wish to state that in deciding in each instance whether the reaction is negative or mildly anaphylactic these facts were kept in mind and where there was any doubt, the result is stated as negative. Where the symptoms were typically anaphylactic, though mild, the results are stated as mild symptoms, and when more pronounced, such as the bucking movements, convulsions, marked drop in temperature, paralysis, etc., the results are stated as symptoms with one or two plus signs depending again on the severity of the symptoms.

Note 2.—I have appreciated from the beginning the necessity of taking every precaution to prevent contamination of the serum used for sensitizing purposes because of the exceedingly small amount necessary to sensitize an animal, and great care has been exercised to prevent such an occurrence. The syringes used to aspirate the blood were kept especially for this work and cleansed by me. The serum was kept in sterile, clean receptacles; the puncture wound made by the hypodermic needle in the stomach and intestines was closed by sutures.

The conditions are such in Experiment 3 that normal digestion cannot proceed and it will be readily seen that a much larger portion of the albumin passed into the circulation within a few hours after its introduction into the stomach. It is not claimed that this is an indication of the fate of albumin in normal digestion, but it indicates that an interference with the process which does not, during the time of experi-

TABLE 3.—EXPERIMENTS IN ANAPHYLAXIS. STOMACHS OF DOGS LIGATED TO INSURE RETENTION OF ALBUMIN

No. of Dog	No. of Guinea-Pig	Sensitizing Dose	Period of Incubation Days	Toxic Dose	Results
523	548	Eight min. dog serum before albumin in stomach	22	1 c.c. egg albumin injected into heart	No symptoms
...	582	Normal	22	1 c.c. egg albumin intravenously	No symptoms
...	549	Eight min. dog serum one hour after albumin in stomach	22	1 c.c. egg albumin intravenously	Mild symptoms
...	550	Eight min. dog serum two hours after albumin in stomach	22	1 c.c. egg albumin intravenously	Symptoms ++ Recovered
...	551	Eight min. dog serum three hours after albumin in stomach	22	1 c.c. egg albumin intravenously	Symptoms ++ Recovered
...	552	Eight min. dog serum five hours after albumin in stomach	22	2.0 c.c. egg albumin intravenously	Symptoms +++
...	554	One c.c. urine from bladder taken five hours after albumin in stomach	22	3 c.c. egg albumin intraperitoneally	Mild symptoms
...	518	One c.c. each serum one, two, three, five hours after albumin in stomach plus 1 c.c. fresh normal dog serum.	22	0.5 c.c. egg albumin intravenously	Symptoms +

Note.—Dog killed after last bleeding; bladder and stomach distended. Blood at five hours' bleeding dark in color and coagulated more quickly than one hour bleeding, although salt solution injected in sufficient quantities to cover fluid loss from bleeding.

ment, seriously injure the vitality of the mucosa, permits the protein to pass through.

In the next experiment a portion of the colon just below the ileocecal valve was ligated and egg albumin injected into the ligated portion.

The results again show (Table 4) a very marked absorption of the albumin without digestion. The conditions are not very different in this experiment from those which might be obtained in a case of intestinal

obstruction. The blood- and nerve-supply to this loop was not seriously disturbed, except in those tissues immediately under the ligature.

In the next experiment the question arose as to whether the ligation of the colon is an important factor in the rapid absorption of the undigested protein. Accordingly, Experiment 4 was repeated, except that

TABLE 4.—Results of Experiment Similar to Previous Ones. Egg Albumin Injected Into Ligated Portion of Colon

No. of Dog	No. of Guinea-Pig	Sensitizing Dose	Period of Incubation Days	Toxic Dose	Results
526	810	One c.c. dog serum before albumin injected	27	1 c.c. egg albumin inj. intravenously	No symptoms
...	977	One c.c. dog serum before albumin injected	27	1 c.c. egg albumin inj. intravenously	No symptoms
...	978	One c.c. dog serum before albumin injected	27	1 c.c. egg albumin inj. intravenously	No symptoms
...	811	One c.c. dog serum one hour after albumin injected	27	1 c.c. egg albumin inj. intravenously	Symptoms +++. Recovered and died five days later
...	813	One c.c. dog serum two hours after albumin injected	27	1 c.c. egg albumin inj. intravenously	Symptoms ++
...	814	One c.c. dog serum three hours after albumin injected	27	1 c.c. egg albumin inj. intravenously	Symptoms ++
...	815	One c.c. dog serum four hours after albumin injected	27	1 c.c. egg albumin inj. intravenously	Symptoms ++
...	816	One c.c. dog serum five hours after albumin injected	27	1 c.c. egg albumin inj. intravenously	Dead in three minutes
...	821	One c.c. urine drawn from bladder six hours after albumin injection	27	1 c.c. egg albumin inj. intravenously	Symptoms +
...	979	One and one-half c.c. dog serum 3 hours after alb. injected.	27	1 c.c. egg albumin inj. intravenously	Symptoms ++
...	980	One c.c. dog serum four hours after albumin injected	27	1 c.c. egg albumin inj. intravenously	Symptoms ++

the egg albumin was injected into the colon below the ileo-cecal valve, but no ligatures were placed about the colon. The abdominal wall was carefully sutured and blood drawn at the intervals indicated. In Table 5 is shown the experimental details.

From these results it is justifiable to conclude that absorption of undigested protein is facilitated by ligation of the portion of the intestine

TABLE 5.—RESULTS IN EXPERIMENT FIVE. TECHNIC SIMILAR TO THAT IN EXPERIMENT FOUR, EXCEPT THAT COLON WAS NOT LIGATED

No. of Dog	No. of Guinea-Pig	Sensitizing Dose	Period of Incubation Days	Toxic Dose	Results
400	449	Two c.c. dog serum before egg albumin injected	23	1 c.c. egg white intravenously	No symptoms
...	463	Two c.c. dog serum before egg albumin injected	23	1 c.c. egg white intravenously	No symptoms
...	475	Two c.c. dog serum one hour after egg albumin injected	23	1 c.c. egg white intravenously	Slight symptoms
...	492	Two c.c. dog serum one hour after egg albumin injected	23	1 c.c. egg white intravenously	Symptoms
...	478	Two c.c. dog serum one hour after egg albumin injected	23	1 c.c. egg white intravenously	Slight symptoms. Dead eight hours
...	420	Two c.c. dog serum two hours after egg albumin injected	23	1 c.c. egg white intravenously	Slight symptoms
...	441	Two c.c. dog serum two hours after egg albumin injected	23	1 c.c. egg white intravenously	No symptoms
...	410	Two c.c. dog serum two hours after egg albumin injected	23	1 c.c. egg white intravenously	No symptoms
...	431	Two c.c. dog serum three hours after egg albumin injected	23	1 c.c. egg white intravenously	No symptoms
...	459	Two c.c. dog serum three hours after egg albumin injected	23	1 c.c. egg white intravenously	No symptoms
...	457	Two c.c. dog serum three hours after egg albumin injected	23	1 c.c. egg white intravenously	No symptoms
...	484	Two c.c. dog serum four hours after egg albumin injected	23	1 c.c. egg white intravenously	No symptoms
...	447	Two c.c. dog serum four hours after egg albumin injected	23	1 c.c. egg white intravenously	No symptoms

into which the protein is injected. These results agree with those obtained in the stomach experiments and demonstrate that obstruction to the normal peristaltic action is an important factor in permitting the passage of foreign albumin through the mucosa. Attention is drawn to the fact that as regards absorption, the ligated loop behaves very much like a Thiry-Vella fistula in a similar portion of the intestine. When a portion of the intestine is denied free access to the secretions formed in other portions of the intestine there is apparently more absorption of the unaltered protein. Since the Thiry-Vella fistula resembles a ligated portion of the intestine in its absorption phenomena, it seems probable

TABLE 6.—ANAPHYLACTIC EXPERIMENTS WITH MILK

No. of Dog	No. of Guinea-Pig	Sensitizing Dose	Period of Incubation Days	Toxic Dose	Results
557	559	Eight min. dog serum **before** milk in stomach	29	1 c.c. milk injected intravenously	No symptoms
...	560	Eight min. dog serum one hour **after** milk in stomach.	29	1 c.c. milk injected intravenously	Mild symptoms
...	561	Eight min. dog serum two hours after milk in stomach.	29	1 c.c. milk injected intravenously	* Dead in four hours
...	564	Eight min. dog serum three hours after milk in stomach	29	1 c.c. milk injected intravenously	Mild symptoms
...	563	Eight min. dog serum five hours after milk in stomach	29	1 c.c. milk injected intravenously	Mild symptoms

* Death probably due to the fact that ether was used during operation on the animal. In no other instance was any anesthetic used.

that the lack of digestive enzymes from other portions of the intestine is quite as potent a factor as the obstruction.

The success of these experiments led me to try the absorption with another form of protein which is one of the most important food-stuffs, namely, milk. Milk is readily digested. The protein of the milk is not as toxic in anaphylactic experiments as that found in the egg or serum proteins, but many experimenters have used it in anaphylactic experiments. The details of the first experiment are given in Table 6.

The milk, in this instance, was put in the stomach through a tube. Physiological conditions prevailed and yet the serum of the dog from one to five hours after the milk was put into the stomach was capable of sensitizing guinea-pigs.

In the next experiment the abdomen was opened, the cardiac and pyloric ends ligated and the milk introduced into the stomach directly through a large hypodermic needle. The experimental details are given in Table 7.

TABLE 7.—Anaphylactic Experiment with Milk. Stomach Ligated at Both Ends and Milk Introduced Directly Through a Needle

No. of Dog	No. of Guinea-Pig	Sensitizing Dose	Period of Incubation Days	Toxic Dose	Results
565	567	Eight min. dog serum before milk in stomach	29	1 c.c. milk injected intravenously	No symptoms
...	568	Eight min. dog serum one hour after milk in stomach	29	1 c.c. milk injected intravenously	Symptoms +
...	570	Eight min. dog serum three hours after milk in stomach	29	1 c.c. milk injected intravenously	Symptoms +
...	582	Eight min. dog serum five hours after milk in stomach	29	1 c.c. milk injected intravenously	Symptoms +
...	573	Eight min. dog serum twenty-four hours after milk in stomach	29	1 c.c. milk injected intravenously	Symptoms +
...	575	One c.c. urine drawn before milk in stomach	29	1 c.c. milk injected intravenously	No symptoms
...	706	Two c.c. urine twenty-four hours after milk in stom.	29	1 c.c. milk injected intravenously	Symptoms +
...	583	Two c.c. urine forty-eight hours after milk in stomach	29	1 c.c. milk injected intravenously	Mild symptoms
...	582	Eight min. dog serum five hours after milk in stomach	29	1 c.c. milk injected intravenously	Symptoms +
...	584	Eight min. dog serum forty-eight hours after milk in stomach	29	1 c.c. milk injected intravenously	Mild symptoms

Note—Dog killed after forty-eight hours' bleeding; stomach greatly distended.

In this case it appears that more of the milk than in the previous experiment must have been absorbed directly into the circulation, for the guinea-pigs were more actively sensitized than before. This corresponds to the finding in the similar experiment with the egg albumin. Evidently when the stomach is prevented from emptying itself, undigested protein is absorbed more readily.

In the next experiment the duodenum was ligated, injected with milk, with the somewhat surprising result shown in Table 8.

The serum taken from two to five hours after milk was introduced did not sensitize guinea-pigs. It seems probable that in the duodenum the digestive action has been sufficient to split the protein to such an extent that it no longer sensitized to the homologous protein.

Since this experiment seems to contradict the results of the experiments with egg albumin reported above, attention may be called to the fact that the portion of the duodenum ligated is well supplied with digestive enzymes; a condition quite contrary to that obtained in lower portions of the intestine.

TABLE 8.—DUODENUM LIGATED AND MILK INJECTED DIRECT

No. of Dog	No. of Guinea-Pig	Sensitizing Dose	Period of Incubation Days	Toxic Dose	Results
518	974	Two c.c. dog serum before	21	5 c.c. milk injected intravenously	No symptoms
...	975	Two c.c. dog serum two hours after milk injected	21	(a) 5 c.c. milk injected intravenously (b) 1 c.c. normal dog serum three days later	(a) No symptoms (b) Symptoms ++
...	976	Two c.c. dog serum two hours after milk injected	21	(a) 5 c.c. milk injected intravenously (b) 1 c.c. normal dog serum three days after	(a) No symptoms (b) Symptoms ++
...	820	Eight min. dog serum five hours after milk injected	21	5 c.c. milk injected intravenously	No symptoms
...	972	Three c.c. urine three hours after milk injected	21	5 c.c. milk injected intravenously	No symptoms

NOTE.—This dog died twelve hours after operation; ligated duodenum greatly distended and ulcerated.

In the next three experiments, Tables 9, 10 and 11, horse serum was used as the antigen.

In Experiment 9 the horse serum was introduced into the stomach through the stomach tube; in Experiment 10 the serum was introduced into the unligated portion of the upper small intestine; in Experiment 11 the antigen was injected into a ligated loop made in about the middle of the small intestine. In Tables 9, 10 and 11 are given the experimental details and results.

From these results it will be seen that there was a slight amount of absorption from the unligated stomach, no absorption from the unligated

TABLE 9.—RESULTS OF EXPERIMENTS IN WHICH HORSE SERUM WAS USED AS THE ANTIGEN INTRODUCED DIRECTLY INTO THE STOMACH

No. of Dog	No. of Guinea-Pig	Sensitizing Dose	Period of Incubation Days	Toxic Dose	Results
402	301	Two c.c. dog serum two hours after horse serum introduced	22	1 c.c. inactivated horse serum intravenously	Slight symptoms
...	323	Two c.c. dog serum two hours after horse serum introduced	22	1 c.c. inactivated horse serum intravenously	Symptoms
...	309	Two c.c. dog serum two hours after horse serum introduced	22	1 c.c. inactivated horse serum intravenously	Slight symptoms
...	319	Two c.c. dog serum two hours after horse serum introduced	22	1 c.c. inactivated horse serum intravenously	Slight symptoms
...	303	Two c.c. dog serum five hours after horse serum introduced	22	1 c.c. inactivated horse serum intravenously	Slight symptoms
...	305	Two c.c. dog serum five hours after horse serum introduced	22	1 c.c. inactivated horse serum intravenously	Slight symptoms
...	307	Two c.c. dog serum five hours after horse serum introduced	22	1 c.c. inactivated horse serum intravenously	Slight symptoms
...	321	Two c.c. dog serum five hours after horse serum introduced	22	1 c.c. inactivated horse serum intravenously	Slight symptoms
...	317	Two c.c. dog serum twenty-two hours after horse serum introduced.	22	1 c.c. inactivated horse serum intravenously	No symptoms
...	315	Two c.c. dog serum twenty-two hours after horse serum introduced	22	1 c.c. inactivated horse serum intravenously	Slight symptoms
...	311	Two c.c. dog serum twenty-two hours after horse serum introduced	22	1 c.c. inactivated horse serum intravenously	No symptoms
...	313	Two c.c. dog serum twenty-two hours horse serum introduced	22	1 c.c. inactivated horse serum intravenously	No symptoms

TABLE 10.—Results of Experiment When Horse Serum Was Introduced Into Unligated Portion of Upper Small Intestine

No. of Dog	No. of Guinea-Pig	Sensitizing Dose	Period of Incubation Days	Toxic Dose	Results
200	363	Two c.c. dog serum one and one-half hours after horse serum injected	23	1 c.c. inactivated horse serum intravenously	No symptoms
...	339	Two c.c. dog serum one and one-half hours after horse serum injected	23	1 c.c. inactivated horse serum intravenously	No symptoms
...	345	Two c.c. dog serum two hours after horse serum injected	23	1 c.c. inactivated horse serum intravenously	No symptoms
...	347	Two c.c. dog serum four hours after horse serum injected	23	1 c.c. inactivated horse serum intravenously	No symptoms
...	341	Two c.c. dog serum four hours after horse serum injected	23	1 c.c. inactivated horse serum intravenously	No symptoms
...	359	Two c.c. dog serum four hours after horse serum injected	23	1 c.c. inactivated horse serum intravenously	No symptoms

Note.—Remainder of series not injected, as one and one-half, two- and four-hour animals were all negative.

TABLE 11.—Results When Antigen Was Injected Into a Ligated Loop of Small Intestine

No. of Dog	No. of Guinea-Pig	Sensitizing Dose	Period of Incubation Days	Toxic Dose	Results
392	783	One c.c. dog serum before horse serum injected	29	1 c.c. horse serum intravenously	No symptoms
...	788	One c.c. dog serum before horse serum injected	29	1 c.c. horse serum intravenously	No symptoms
...	784	One c.c. dog serum one hour after horse serum injected	29	1 c.c. horse serum intravenously	Symptoms +
...	785	One c.c. dog serum one hour after horse serum injected	29	1 c.c. horse serum intravenously	Symptoms +
...	790	One c.c. dog serum two hours after horse serum injected	29	1 c.c. horse serum intravenously	Symptoms ++

upper intestine and marked absorption from the ligated loop. In practically all respects these three experiments show that horse serum behaves like egg albumin in its absorption capacities.

In the next two experiments beef serum was used as an antigen. In both instances the serum was injected into the ligated lower portion of the ileum. Since the results of the two experiments were identical, only one will be quoted. The results are seen in Table 12.

The results of this experiment are identical with those in which other proteins were used as antigens.

TABLE 12.—Results of Experiment in Which Beef Serum Antigen Was Injected Into Ligated Lower Portion of Ileum

No. of Dog	No. of Guinea-Pig	Sensitizing Dose	Period of Incubation Days	Toxic Dose	Results
833	897	Two c.c. dog serum before beef serum injected	25	1.5 c.c. beef serum intravenously	No symptoms
...	898	Three c.c. dog serum before beef serum injected	25	1 c.c. beef serum intravenously	No symptoms
...	899	One c.c. dog serum before beef serum injected	25	1 c.c. beef serum intravenously	No symptoms
...	211	Normal guinea pig	25	1 c.c. beef serum intravenously	No symptoms
...	900	One c.c. dog serum one hour after beef serum injected	25	1 c.c. beef serum intravenously	Symptoms +
...	894	Two c.c. dog serum one hour after beef serum injected	25	1 c.c. beef serum intravenously	Symptoms +
...	895	One c.c. dog serum two hours after beef serum injected	25	1 c.c. beef serum intravenously	Dead in five minutes
...	892	Two c.c. dog serum two hours after beef serum injected	25	1 c.c. beef serum intravenously	Dead in fifteen minutes

All of the proteins used in the experiments thus far reported have been of animal origin, and it is quite possible that vegetable proteins may not have the same absorption behavior as those of animal origin. In the two following experiments, edestin[16] was used as the antigen. Two experiments were made, in both of which the solution of edestin was injected into the ligated lower portion of the ileum. Since the two experiments agree as to results, only one of them will be quoted. In Table 13 is given the details of one of these experiments.

16. The edestin used in these experiments was prepared by Dr. Martha Tracy in Professor Mendel's laboratory.

From the results recorded above, one point is evident: the absorption of the edestin is accomplished more slowly than in the case of the animal antigens. The symptoms given by pigs sensitized with the blood drawn during the earlier hours following the injection are mild; the severer symptoms are given by pigs sensitized with blood drawn four hours after the introduction of the antigen. The reason for this is probably the slow

TABLE 13.—RESULTS OF EXPERIMENT IN WHICH EDESTIN IN SOLUTION WAS INJECTED INTO LIGATED LOWER PORTION OF ILEUM

No. of Dog	No. of Guinea-Pig	Sensitizing Dose	Period of Incubation Days	Toxic Dose	Results
434	438	One c.c. dog serum before edestin injected	23	1 c.c. edestin injected intravenously	No symptoms
...	440	One c.c. dog serum before edestin injected	23	1 c.c. edestin injected intravenously	No symptoms
...	442	One c.c. dog serum before edestin injected	23	1 c.c. edestin injected intravenously	No symptoms
...	444	Two c.c. dog serum one hour after edestin injected	23	1 c.c. edestin injected intravenously	Mild symptoms
...	446	Two c.c. dog serum two hours after edestin injected	23	1 c.c. edestin injected intravenously	Mild symptoms
...	448	Two c.c. dog serum two hours after edestin injected	23	1 c.c. edestin injected intravenously	Mild symptoms
...	450	Two c.c. dog serum three hours after edestin injected	23	1 c.c. edestin injected intravenously	Mild symptoms
...	452	Two c.c. dog serum three hours after edestin injected	23	1 c.c. edestin injected intravenously	Mild symptoms
...	454	Two c.c. dog serum three hours after edestin injected	23	1 c.c. edestin injected intravenously	Mild symptoms
...	456	Two c.c. dog serum four hours after edestin injected	23	1 c.c. edestin injected intravenously	Mild symptoms
...	458	Two c.c. dog serum four hours after edestin injected	23	1 c.c. edestin injected intravenously	Symptoms +
...	460	Two c.c. dog serum four hours after edestin injected	23	1 c.c. edestin injected intravenously	Symptoms +

Note 1.—Total mg. edestin injected into loop —2,750 mg. protein.

Note 2.—Dog killed and autopsied after last (four hours) bleeding. Ligated portion empty except for small quantities of fecal matter.

Note 3.—Sixty c.c. blood drawn; 90 c.c. NaCl injected in two portions at second and third bleedings. Blood at third and fourth bleedings dark in color and clotted very quickly.

absorption of the antigen, which is probably due to the fact that soon after the solution was introduced into the intestine it was precipitated. Other investigators have noted that edestin is readily precipitated from its solution.[10]

In the following experiment a point which is somewhat incidental to the main question has been subjected to experimental investigation. In the first experiments which were made on this topic, a preliminary report of which has already been published, I found that egg albumin could be detected in the blood for three days after the time of injection, but not beyond this time. It seemed advisable to further test this observation with two types of protein, edestin and horse serum. In the first experiment edestin was used as the antigen. Fifty cubic centimeters of a solution containing altogether 3.1 gm. of protein was injected into the jugular vein of a dog. The animal was bled three, six, ten, thirteen and sixteen days after the injection was made. Further experimental details are given in Table 14.

From this table it may be seen that the only pigs that were sensitized to the edestin were those receiving blood withdrawn three days after the injections were made. It follows that the edestin must have remained in the dog's circulation for a period of at least three days, but not as long as six days.

Both egg-white and edestin are proteins so different in structure from blood serum that it is quite possible that they might be removed from the circulation in a shorter time than a serum protein from another species of animal. After an injection of diphtheria antitoxin antibodies have been found in the blood as late as three weeks after the injection. The length of time in which horse serum would remain in the circulation of the dog was tested on three different dogs. Fifty cubic centimeters of horse serum were injected into the jugular vein. Blood was drawn at different periods up to forty-nine days and used to sensitize guinea-pigs. Inasmuch as the dog may have become immune to the antigen, it was necessary in this case to test for passive anaphylaxis. The experimental details in one case are given in Table 15.

Attention is called to the fact that six pigs sensitized with the serum drawn forty-nine days after horse serum was injected into the dog were tested for passive anaphylaxis, but only one showed any symptoms. These were very mild, while four other pigs that were allowed to incubate for a period of forty-one days, when tested for active anaphylaxis showed marked reactions, one of them dying in ten minutes.

It seems probable that the horse serum has remained in the dog's circulation unaltered during this time.

The behavior of the horse serum is distinctly different from that of the edestin or the egg albumin. It would seem that these latter proteins

are much more promptly attacked and removed from the circulation than is serum protein.

This experiment is somewhat similar to that of Gay and Southard,[17] who bled guinea-pigs that had been previously used in diphtheria anti-

TABLE 14.—EXPERIMENT WITH EDESTIN AS ANTIGEN TO DETERMINE HOW LONG THE FOREIGN PROTEIN REMAINED IN THE BLOOD

No. of Dog	No. of Guinea-Pig	Sensitizing Dose	Period of Incubation Days	Toxic Dose	Results
505	423	Two c.c. dog serum ten days after edestin injected	6	1.5 c.c. solution edestin inj. intravenously	No symptoms
...	401	One c.c. dog serum before edestin injected	46	1 c.c. edestin injected intravenously	No symptoms
...	403	One c.c. dog serum before edestin injected	46	1 c.c. edestin injected intravenously	No symptoms
...	405	One c.c. dog serum before edestin injected	46	1 c.c. edestin injected intravenously	No symptoms
...	407	Two c.c. dog serum three days after edestin injected	46	1 c.c. edestin injected intravenously	Mild symptoms
...	409	Two c.c. dog serum three days after edestin injected	46	1 c.c. edestin injected intravenously	Mild symptoms
...	411	Two c.c. dog serum three days after edestin injected	46	1 c.c. edestin injected intravenously	Mild symptoms
...	413	Two c.c. dog serum six days after edestin injected	46	1 c.c. edestin injected intravenously	No symptoms
...	415	Two c.c. dog serum six days after edestin injected	46	1 c.c. edestin injected intravenously	No symptoms
...	417	Two c.c. dog serum six days after edestin injected	46	1 c.c. edestin injected intravenously	No symptoms
...	423	Two c.c dog serum ten days after edestin injected	46	1 c.c. edestin injected intravenously	No symptoms
...	167	Two c.c. dog serum thirteen days after edestin injected	46	1 c.c. edestin injected intravenously	No symptoms
...	210	Two c.c. dog serum thirteen days after edestin injected	46	1 c.c. edestin injected intravenously	No symptoms

toxin experiments, 204 and 169 days after their injection of horse serum, and injected this serum into other normal guinea-pigs. Fifteen days later the pigs were injected with horse serum with fatal results. Since

17. Gay and Southard: Jour. Med. Research, 1907, xvi, 143.

TABLE 15.—Experiment with Horse Serum as Antigen to Determine How Long the Foreign Protein Remained in the Blood

No. of Dog	No. of Guinea-Pig	Sensitizing Dose	Period of Incubation Days	Toxic Dose	Results
320	109	Two c.c. dog serum thirty-one days after horse serum injected	1	1 c.c. horse serum intravenously	No symptoms
...	945	Two c.c. dog serum thirty-one days after horse serum injected	2	1 c.c. horse serum intravenously	No symptoms
...	308	Two c.c. dog serum thirty-one days after horse serum injected	2	1 c.c. horse serum intravenously	No symptoms
...	502	Two c.c. dog serum thirty-one days after horse serum injected	3	1 c.c. horse serum intravenously	No symptoms
...	264	Two c.c. dog serum before horse serum injected	25	1 c.c. horse serum intravenously	No symptoms
...	952	Two c.c. dog serum before horse serum injected	25	1 c.c. horse serum intravenously	No symptoms
...	880	Two c.c. dog serum before horse serum injected	25	1 c.c. horse serum intravenously	No symptoms
...	571	Two c.c. dog serum thirty-one days after horse serum injected	25	1 c.c. horse serum intravenously	Symptoms +
...	927	Two c.c. dog serum thirty-one days after horse serum injected	25	1 c.c. horse serum intravenously	Symptoms +
...	946	Two c.c. dog serum thirty-one days after horse serum injected	25	1 c.c. horse serum intravenously	Symptoms ++
...	847	Two c.c. dog serum forty-nine days after horse serum injected	4	1 c.c. horse serum intravenously	No symptoms
...	212	Two c.c. dog serum forty-nine days after horse serum injected	4	1 c.c. horse serum intravenously	Symptoms (?)
...	162	Two c.c. dog serum forty-nine days after horse serum injected	41	1 c.c. horse serum intravenously	Symptoms +
...	839	Two c.c dog serum forty-nine days after horse serum injected	41	1 c.c. horse serum intravenously	Symptoms +
...	968	Two c.c. dog serum forty-nine days after horse serum injected	41	1 c.c. horse serum intravenously	Symptoms ++
...	705	Two c.c. dog serum forty-nine days after horse serum injected	41	1 c.c. horse serum intravenously	Died in ten minutes

Note—As the serum of the six-, ten- and thirteen-day pigs was negative, the sixteen-day pigs were not intoxicated.

the authors did not test these pigs for passive sensitization, and since it is known that passive sensitization with the serum of an homologous animal lasts for a long time, there is no reason to suppose that the experimental pigs were not passively rather than actively sensitized. In our case, however, it is known that the active sensitization was much stronger than the passive sensitization.

SUMMARY

1. These experiments demonstrate that protein may be absorbed unaltered through the intact epithelium of the gastro-intestinal tract.

2. Conditions which interfere with normal digestive function, such as ligaturing a portion of the intestine, or the whole stomach, or the isolation of a portion of the intestine as a Thiry-Vella fistula, markedly increase the amount of protein absorbed.

3. The amount of protein absorbed without digestion under physiological conditions is too small to be of any significance as a factor in nutrition.

4. Edestin and egg albumin when injected intravenously into a dog do not remain in the circulation in a condition to sensitize guinea-pigs for a long period; in our experiments for three days. On the other hand, horse serum may be detected in the dog's circulation for a period of at least forty-nine days.

5. The absorption in the duodenum differs from that in other portions of the intestine in that the ligation of the duodenum does not facilitate absorption of unaltered protein.

Although the amount of unaltered protein concerned in this reaction is not large, it may, nevertheless, be of decided import. Only a very small amount of protein is required to sensitize an animal, or seriously intoxicate a sensitive animal. Certain pathological conditions may have their origin in the fact that the absorbed protein has caused certain toxic reactions. The relation between anaphylaxis and asthma has been pointed out many times. It is well known that asthmatic persons are often particularly sensitive to certain food-stuffs. Many skin conditions are classed by dermatologists as anaphylactic in their nature.[18] There is considerable possibility that these experiments offer an explanation for such manifestations. Certain food intoxications, and some of the symptoms of intestinal obstruction, may be in part dependent on the absorption of unaltered protein.

18. Johnson: Jour. Cutan. Dis., 1912, xxx, 136.

THE CHOLESTEROL AND CHOLESTEROL-ESTER CONTENT OF THE BLOOD IN XANTHOMA TUBEROSUM MULTIPLEX *

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I. INTRODUCTION

In recent years considerable interest has been shown regarding the rôle that cholesterol and its esters play in the body. Cholesterol was first noted by Conradi in 1775 and by Gren in 1788, to be present in gall-stones, and they called this substance "gall-stone fat." Fourcroy subsequently classified it along with spermaceti and adipocere. Chevreul, in 1815, demonstrated certain differential qualities of this substance and called it cholesterin.

This substance, now preferably called cholesterol ($C_{27}H_{44}O$, H_2O), is a mono-hydroxy terpeno-alcohol and forms esters with fatty acids in the same manner as does the tri-hydroxy alcohol glycerol. The esters of cholesterol with oleic and palmitic acids exist preformed in animal tissues, while that with stearic acid has not been identified positively in organisms. Bondet, in 1883, found cholesterol-oleate in the blood-serum and called it "seroline," but Hürthle, in 1895, was the first to identify and study the substance. This ester has also been found normally and pathologically in many portions of the body, in the kidneys, liver, arteriosclerotic arteries, etc., but is absent from the brain.

Some of the esters of cholesterol show a crystalline fluid phase (fluid crystals) and the identification of such substances by Kaiserling and Orgler[1] first directed modern attention to this peculiar phenomenon. They have also been carefully studied by Aschoff,[2] Adami,[3] Kawamura[4] and others.

In view of the fact that several observers have considered an excess of cholesterol esters in the blood to be present in the condition called xanthoma tuberosum multiplex, I thought it would be of considerable

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* From the Biochemical Laboratory of the Western Pennsylvania Hospital, Pittsburgh, Pa.

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1. Kaiserling and Orgler: Virchows Arch. f. path. Anat., 1902, clxvii; Berl. klin. Wchnschr., 1910, xlvii, 2156; Deutsch. med. Wchnschr., 1910, 1466.

2. Aschoff: Beitr. z. path. Anat., 1910, xlvii, 1.

3. Adami: The Myelins and Potential Fluid Crystalline Bodies of the Organisms, The Harvey Lectures, 1908, No. 2, p. 117.

4. Kawamura: Die Cholesterinesterverfettung, Jena., 1911.

interest to attack this problem from an experimental standpoint, especially as the new method of Windaus for the estimation of the cholesterol and cholesterol-esters is very accurate, and also because in my case the samples of blood were collected for analysis during the time when new xanthoma lesions were forming, giving every reason to suppose that if the condition was characterized by an excess of cholesterol esters in the blood, this would be the most favorable time to find the same.[5]

I would also draw attention to the fact that in my work, a "control" was studied. This person was convalescent from an attack of gonorrheal arthritis, and for two days previous to the collection of the blood was taking the same diet as the patient with xanthoma tuberosa multiplex.

II. REVIEW OF LITERATURE

Pinkus and Pick[6] made studies of the common flat xanthoma of the eyelids; xanthoma tuberosum diabeticum, xanthoma tuberosum in diabetes and xanthoma tumor, a large isolated tumor. Pathologically, they found each of these types to be composed of the same cellular elements and that microchemically and microphysically they were identical. Examination of unstained frozen sections hardened in formaldehyd solution showed the entire tissue to be filled with fine needle-like crystals which showed the phenomena of "anisotropism" when examined under a polarizing microscope. With osmic acid there was almost no blackening. Sudan III stained the tissue red or brown-red.[7]

They concluded that the characteristic substance of xanthomas is not fat, but the doubly refracting substance. They think it resembles the so-called "protagon" and is a cholesterol-ester, which substance is supposed to be found in the blood in icterus and diabetes in greatly increased amounts and that the deposition of this substance in the tissues produces the formation of xanthoma.

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5. I wish to thank Dr. H. Fox, dermatologist to the German Hospital, New York, for his kindness in placing the patient at my disposal. The samples of blood were collected and the drying of the same was done at the German Hospital. The rest of the work was carried out in Pittsburgh.

6. Pinkus and Pick: Deutsch. med. Wchnschr, 1908, xxxiv, 1426; Monatsch. f. prakt. Dermat., 1908, xlvi; Arch. f. Derm., 1908, cxii, 228.

7. Through the kindness of Dr. S. Pollitzer I had the opportunity of studying certain properties of the coloring matter present in the xanthoma cell. The material used was obtained at biopsy from Dr. Pollitzer's patient. It was ground up with sand and when treated with ether, imparted a golden color to the ether. This solution gave all the color reactions typical of lipochromes, and readily diffused from ether through a rubber membrane into ether, a property which I have found lipochromes to possess. Exposure of an ethereal solution of this lipochrome to direct sunlight for a period of three hours caused complete disappearance of the color, and on adding various oxidizing agents, the color did not return. For the above reasons we can conclude that this coloring matter is a true lipochrome.

Pringsheim[8] examined xanthomatous tissues from the skin and dura mater chemically and found that certain acetone-soluble crystals present were free from nitrogen and phosphorus and gave all the reactions peculiar to cholesterol, and that they had a constant melting point. He believes this substance to be the same as that described by Pinkus and Pick and also thinks that the substance is deposited in xanthoma by cholesterol from the blood.

Chauffard and Laroche[9] claim that xanthoma is probably caused by an increase of greater or less duration in the cholesterol content of the blood-serum, and conclude, therefore, that it is a sign of lipolytic insufficiency of the pancreas and is less to be regarded as a tumor than as a local reaction of the skin to the cholesterol present in the blood-serum.

Pollitzer and Wile[10] have found in the earliest lesions of xanthoma, an infiltration of the perivascular and intercellular lymph-spaces with a fatty substance, which is present to a considerable extent also in the new-formed cells, and in the endothelium of the capillaries and here and there in the basal layer of the epidermis. The xanthoma giant cells on staining with osmic acid or Sudan III are found to be almost entirely filled with a fatty substance. This substance was also soluble in alcohol. On examination of fresh sections of xanthoma by polarized light, they found that at least a greater portion of the fatty substance contained in the cells presented the phenomena of anisotropism. They think it likely that in cases associated with an excess of lipins in the blood, that the lipins in excess pass out through the capillaries of the skin at some point of lessened resistance, and their presence in the perivascular connective tissue cells appears to act as a stimulus and causes a proliferation of these cells, which take up the lipins poured out from the blood-vessels and form the xanthoma cells.

They concluded that xanthoma tuberosum represents an irritative connective-tissue hyperplasia, in which the extravasation of cholesterol fatty acid-ester present in excess in the blood serves as the stimulus, and that certain connective tissue cells which take up these substances proliferate and increase in size, forming the typical xanthoma cells.

III. COLLECTION AND ANALYSES OF THE BLOOD

The blood was obtained from the median basilic vein by means of a Wassermann needle. It was collected in a weighed bottle containing ammonium oxalate to prevent coagulation, the increase in weight of the bottle giving the amount of blood collected. The blood was then cen-

8. Pringsheim: Deutsch. med. Wchnschr., 1908, xxxiv, 2145; Biochem. Ztschr., 1908, xv, 52.
9. Chauffard and Laroche: Zentralbl. f. Biochem. u. Biophys., 1912, xiii, 102.
10. Pollitzer and Wile: Jour. Cutan. Dis., 1912, xxx, 235.

trifuged, and the corpuscles washed thoroughly with physiological salt solution and the washings added to the plasma. The corpuscles and plasma were then dried separately by means of anhydrous sodium sulphate, placed in a Soxhlet extractor and extracted with anhydrous ether, followed by extraction with alcohol and then with ether, until all the ether and alcohol soluble substances were extracted.

The extracts were evaporated in a weighed dish at 35 C., and then placed in a vacuum desiccator with sulphuric acid until of constant weight. The cholesterol and cholesterol-esters present were then estimated by the excellent method of Windaus.[11]

TABLE SHOWING CHOLESTEROL AND CHOLESTEROL-ESTER CONTENT OF THE BLOOD PER 100 GRAMS OF BLOOD*

Case	Blood Corpuscles		Blood Plasma	
	Cholesterol, Per Cent.	Cholesterol-Ester, Pct.	Cholesterol, Per Cent.	Cholesterol-Ester, Pct.
Xanthoma tuberosa multiplex†	0.065	*trace*	0.048	0.022
Control‡	0.068	*trace*	0.046	0.028

* Cholesterol-ester figures are in terms of the stearate.
† 26.8670 grams of blood used for the analyses.
‡ 25.4104 grams of blood used for the analyses.

The accompanying table contains the results obtained in this study, showing that in the case of xanthoma tuberosum multiplex studied, there was *no increase in the amount of cholesterol or of cholesterol-esters in the corpuscles or plasma when compared with the corpuscles and plasma of a normal person as a control.*

The writer wishes to thank Dr. F. M. Hanes for giving him the expensive digitonin that was used in this method of estimation of these substances.

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11. Windaus: Ber. d. deutsch. chem. Gesellsch., 1909, xlii, 238; Ztschr. f. physiol. Chem., 1910, lxv, 110.

THE RELATION OF FATIGUE TO PARALYSIS LOCALIZATION IN PLUMBISM *

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The apparent predilection of lead and its salts for the extensor muscles of the wrist, or the musculospiral nerve which supplies them, has for a long time remained unexplained.

This peculiar localization, as well as changes in the muscles themselves, has formed subject matter for numerous hypotheses. One of the oldest views, which is now almost obsolete, held that the paralysis was due to intramuscular changes. The spinal view was held by Remak and Erb, but the preponderance of opinion at present points to the peripheral nerves as the most likely origin, and even Remak himself admits the lack of convincing testimony in favor of the spinal origin. "The constancy of peripheral changes and the infrequency of noteworthy changes in the cord make the peripheral the more probable theory; but if it is correct, there is yet no explanation of the almost regular escape of certain muscles from the paralysis."[1]

With the hope of elucidating this interesting point, Dr. Warthin suggested that I make an attempt to corroborate the view which is known as Edinger's theory. He explains these peculiar saturnine paralyses as the result of excessive strain on certain groups of muscles. In this way, he accounts for the common wrist drop.

His conclusions are as follows:

(a) Of the forearm, the flexors (triceps, anconeus, extensors, biceps, brachialis anticus and supinator longus) possess a high degree of capacity for work; while the supinators are characterized by great mass, and are brought into play mainly in work of coarse and heavy nature, and not during fine manipulation.

(b) The muscles concerned in pronation are of small capacity for work, and are not called on for sustained work. As for the muscles acting on the wrist and hand, he concludes that the extensors (carpi radialis longior and brevior, carpi ulnaris and the extensors of the fingers) are powerful, and much exceed in capacity for work the flexors (flexor carpi radialis, flexor carpi ulnaris, the flexors of the fingers, etc.), but in all fine manual work, and especially where close grasping move-

* Submitted for publication July 10, 1913.
* From the Pathological Laboratory, University of Michigan.

1. Edsall: Osler's Modern Medicine, i, 96.

ments enter into association with the flexors, external strain is put on them, while the flexors merely support their action. The extensor communis digitorum is the weakest of all the long finger muscles; its volume is hardly one-fourth that of the corresponding flexor, and while it acts only on the first of the phalanges, the flexors act on all three. In all fine work they are called on for heavy strain, especially the interossei and the lumbricales, but in harmony with the long flexors when grasping movements are performed. The small muscles of the fingers have nearly the same mass as the extensor communis, and in all fine movements or grasping efforts are taxed severely; but their play is under considerably more favorable physical relations than that of the extensors, while at times they are aided by the long flexors. The chief adductor muscle of the thumb (extensor metacarpi pollicis) is particularly powerful; the other extensors of the thumb are very weak and work under unfavorable physical conditions, but are supported in their action by the strong adductor muscle. The muscles of the abductor opponens and flexor brevis in the complicated work thrown on the thumb in manipulation are much exerted, so that the effects of over-exertion show themselves first in this region.

Thus Edinger maintains that the muscle-supply of the arm is designed for heavy work, the muscles of the finger and hand having to carry more work than can be expected of them from a consideration of their volume and physical action.

Teleky[2] reviews forty cases of paralysis with special reference to this theory. Thirteen were cases of the antibrachial type of D'jerine-Klumpke. In only one was the left hand affected, while in all the others except one, the right hand was affected. In it both hands suffered. These facts are significant in their relation to causation by employment.

The paralysis of the small muscles of the hand is rather characteristic in file cutters. As is known, these muscles are used predominately in this trade. Goadby and Legg[3] have frequently observed the decrease in size of the thumb and hypothenar eminences in lead rollers.

Of fourteen painters suffering from plumbism, Teleky[2] found three with paralysis of the right forearm only, while the remainder had both arms affected, but always more marked in the right than in the left. In some of these, the shoulder muscles were paralyzed, owing to the strain caused by raising the arms above the head, or lying on the back to paint the running gears of carriages.

Particularly interesting are the cases cited by Teleky in lead capsule polishers. These cases showed right-sided paralysis of the adductor brevis pollicis supplied by the median nerve, and partial paralysis of the

2. Teleky: Deutsch. Ztschr. f. Nervenheilk, 1909, xxxvii.
3. Goadby and Legg: Lead Poisoning and Lead Absorption, Longmans & Co.

long extensors and of the extensor ossis metacarpi pollicis supplied by the radial nerve, and in one or two cases complete paralysis of the thenar muscles, and adductor, while the extensors of the fingers and wrists were only partially paralyzed. This unusual muscular involvement is undoubtedly the result of the peculiar movement necessary in polishing the capsules of bottles on a revolving spindle, involving especially the use of the opponens muscle.

Teleky reports a shoemaker who was poisoned with white lead. He developed not only paralysis of the adductors and extensors of the thumb, but also a paralysis of a lower extremity. He explains the latter by the exertion thrown on the adductor muscles of the thigh while holding the shoe.

In children affected with lead palsy the frequency of paraplegia has often been noticed. Both Oliver[4] and Goadby and Legg,[3] as well as Escherich and Variot[5] make mention of it.

I have to report as an original clinical observation, a painter, who, when plying his trade, had more climbing of ladders and mixing of paints to do than actual work with the brush. He developed muscular weakness and paraplegia some time before developing the wrist drop.

Goadby and Legg[3] have poisoned cats experimentally, and found that the quadriceps extensor muscles supplied by the anterior crural nerve was the first group affected, while soon after the lumbar group of spinal muscles was involved. This selection is significant, considering that these are the groups used in jumping movements.

These observers have also found hemorrhages in the nerve (anterior crural) and consider the minute hemorrhages resultant on the degeneration of the venioles to be of paramount importance in the pathology of lead poisoning.

From these observations from varied sources, one fact stands out rather strikingly — there is no necessary anatomical relationship of the paralysis in plumbism, but the functional relationship of involved muscles seems essential.

Gombault[6] sought to explain the paralysis of the hand and arm muscles by the absorption of lead through the skin, but this hypothesis is rather absurd when we come to account for the ocular or shoulder paralysis, or even that of the lower extremities.

Quoting from Alice Hamilton's article,[7] Labbe is authority for the statement that storage battery workers suffer from paralysis of the shoulder muscles. Bernhardt and Leichtentritt speak of the paralysis

4. Oliver: "Occupational Pathology."
5. Escherich and Variot: Jour. Am. Med. Assn., 1911, lvi, 1240. Quoted in Alice Hamilton's Article.
6. Gombault: Arch. Physiol., 1873.
7. Hamilton, Alice: Jour. Am. Med. Assn., 1911, lxi, 1240.

of the left fingers and thumb in file makers who grasp the chisel with the left hand.

Patch[8] relates a case of marked atrophy and paralysis of the shoulder muscles in a man who ran a "delicatessen." He was accustomed to do much lifting and first noticed that he was not able to lift as much as formerly. He presumably contracted the disease by substitution of a lead pipe in the connections of his soda fountain. C. H. Snover[9] of Randolph, N. Y., reports a case of a 16-year-old girl who sealed cans in a milk condensery. He says in part:

> With arms extended, there was a marked wrist drop, especially on the right. The patient used the right hand to use the soldering iron. The left hand could be extended to bring it in line with the forearm, but no more, and this only with difficulty. No extension was possible in the right hand.

Since the fatigue basis has such logical clinical verification, Dr. Warthin thought it wise to ascertain what could be accomplished experimentally to validate this claim.

A. DETERMINING THE SUSCEPTIBILITY OF THE FROG TO NEUTRAL LEAD ACETATE. (FROGS 1 AND 2)

	Date	Amount of Lead Given	Notes
Frog 1..... Wt. 30 gm.	11/15/12	One c.c. sat. aqueous neutral lead acetate into dorsal lymph-sac.	11:30 a. m. Moderate stupor and diminution of reflexes.
	11 a. m.	All structures in right thigh ligated except the sciatic nerve. Frog pithed. Reflex irritability soon recovered.	12:00 m. Increase of stupor. Crossed reflexes negative. 1 p. m. Reflexes disappeared. 1:30 p. m. Death, as determined by cessation of circulation in the web of the foot. Reaction to weak induction shock. Stimulation of the right and left gastrocnemii, both directly, and by way of the sciatic nerve is positive.
Frog 2..... Wt. 27 gm.	11/15/12	Two c.c. neutral lead acetate into dorsal lymph-sac.	2:15, stupor and reflex diminution.
	2 p. m.	Same as above.	2:30 marked stupor. Cross reflexes negative. 3:00, increase of stupor. 3:45, death. Reaction to weak induction shock same as above.

8. Patch: Boston Med. and Surg. Jour., 1909, 653.
9. Snover, C. H.: Jour. Am. Med. Assn., 1911, lvi, 1799; case report.

In these experiments, frogs were the animals selected, because they were most convenient for stimulation and because the results of fatigue could be accurately computed in a mechanical way. It was first necessary to determine their susceptibility to a soluble salt of lead, and also interesting to determine its sphere of action. To this end the Curare Experiment was performed with lead acetate. Briefly, this consists in ligation of all the structures of the thigh, excepting the sciatic nerve, and then the injection of the poison into the dorsal lymph-sac.

B. Determining the Minimum Lethal Dose of Neutral Lead Acetate in Frogs. Frogs Three to Eight, Inclusive.

SERIES ONE

	Date	Amt. of Lead Into Dorsal Lymph-Sac c.c.	Results
Frog 3 ..... Wt. 28 gm.	11/17/12 8 a. m.	0.25	Negative at any time.
Frog 4	11/17/12 8 a. m.	0.50	9 a. m., stupor and diminution of reflex, which gradually abated and frog finally recovered.
Frog 5 ..... Wt. 30 gm.	11/17/12 8 a. m.	0.75	9 a. m., stupor and reflex diminution. 10 a. m., stupor marked. Condition grew progressively worse until 3 p. m., when frog died.

SERIES TWO

Frog 6 ..... Wt. 27 gm.	11/18/12 8 a. m.	0.5	Same as 4
Frog 7 ..... Wt. 29 gm.	11/18/12 8 a. m.	0.6	11 a. m., slight stupor. 12 m., increase. 6 p. m., dead
Frog 8 ..... Wt. 30 gm.	11/18/12 8 a. m.	0.7	10 a.m., slight stupor. 11 a.m., marked stupor. 3 p. m., dead.

0.6 c.c. saturated aqueous solution neutral lead acetate is M. L. D. for 30 gm. frog; or 0.02 c.c. per gm.

Two c.c. saturated solution of lead acetate were so injected into a 25-gm. frog, which killed it in about two hours. The animal failed to respond to reflex stimulation, this failure being of gradual development. Direct application of the electrodes to the muscles provoked a marked response. Stimulation of the sciatic nerves also produced marked muscular contraction. At no time were any crossed reflexes observed. This experiment proves that the frog is susceptible to lead acetate, and that it does

C. Determining the Results of Fatigue Produced by the Direct Method in Lead Poisoned Frogs. Frog 9. Weighed 25 Gm.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
12 /2/12 5 p. m.	0.5	15″	10½	Stimulation applied to right gastrocnemius muscle; an electrode at either end.
12/ 3/12	...	15″	10½	Frog shows stupor.
12/ 4/12	...	...	....	Reacts poorly.
12/ 4/12	...	14″	10½	Stupor. Reacts poorly.
12/ 6/12	...	...	....	Frog normal again.
12/ 7/12	...	15″	10½	Induration at electrodal points.
12/ 8/12	...	13″	10½	
12/ 9/12	...	13″	10½	Stupor.
12/10/12	...	...	....	Frog dead.

Reaction to Induction Shock:

Gastrocnemii, direct application:

Right negative to weak current; positive to strong current.

Left at 10½ negative; 9 cm. positive.

Sciatics: Positive at 10½. Right gastrocnemius shows 97.3 gm. millimeters of work; left, 112.4 gm. millimeters of work.

Frog 10. Control to Frogs 9 to 20. Weight 28 Gm.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
12/ 2/12	...	15″	10½	Stimulation applied to right gastrocnemius an electrode at either end.
12/ 3/12	...	15″	10½	
12/ 4/12	...	15″	10½	
12/ 6/12	...	Rest	....	
12/ 7/12	...	13″	10½	Induration at electrodal points.
12/ 8/12	...	12″	10½	
12/ 9/12	...	14″	10½	
12/10/12	...	...	....	Frog killed.

Reaction to Induction Shock:

Gastrocnemii, direct application:

Right at 10½ cm. weak; at 9 cm. strong.

Left at 12 cm. strong.

Right gastrocnemius, 132.6 gm. millimeters of work; left, 252.4 gm. millimeters.

not perceptibly affect the muscles directly, the end plates or the peripheral nerves. Since the animal's brain was destroyed by pithing, by exclusion we arrive at the fact that in the frog the spinal cord is the sphere of action of lead, given in doses sufficient to produce acute effects. (See Section A, Frogs 1 and 2, Protocol of Experiments.)

FROG 11. WEIGHT 30 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
12/ 4/12	0.35	12″	10	Direct Stimulation of right gastrocnemius.
12/ 5/12	...	13″	10	
12/ 6/12	...	12″	10	Moderate stupor.
12/ 7/12	...	12″	10	Moderate stupor.
12/ 8/12	...	12″	10	
12/ 9/12	...	12″	10	
12/10/12	...	...	....	Killed frog.

Reaction to Induction Shock:

Gastrocnemii, direct application:

Right, 10 negative and 9½ negative; 8 cm. positive.

Left, 10 cm. negative; 9 cm. positive.

Sciatics: Positive at 10½ cm. Right gastrocnemius, 107 gm. millimeters of work; left, 117.5 gm. mil. of work.

FROG 12. WEIGHT 30 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
12/ 6/12	0.3	12″	10	Direct stimulation of right gastrocnemius.
12/ 7/12	...	12″	10	
12/ 8/12	...	12″	10	
12/ 9/12	...	12″	10	
12/11/12	...	12″	10	
12/12/12	...	12″	10	
12/13/12	...	12″	10	
12/14/12	...	12″	10	
12/15/12	...	12″	10	Killed frog.

Reaction to Induction Shock:

Practically the same as in No. 11.

Work: Right gastrocnemius, 104.3 gm. mil.; left, 119.1 gm. mil.

A saturated aqueous solution of neutral lead acetate was used exclusively in all the experiments, because it is the most soluble salt. It was always injected into the dorsal lymph-sac. The weight of the frogs was always between 25 and 35 gm.

It was next necessary to determine the minimum lethal dose of lead acetate for these animals. (See Protocol of Experiments, Section B, Frogs 3 to 8, inclusive.) In Series I of three frogs, Frog 3 was given 0.25 c.c. of the lead solution, and the dose progressively increased by an increment of 0.25 c.c. in the remaining two. The first two frogs of the

FROG 13. WEIGHT 25 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
12/ 9/12	...	13″	10	Direct stimulation of
12/10/12	...	13″	10	right gastrocnemius.
12/11/12	...	13″	10	
12/12/12	...	13″	10	
12/13/12	...	13″	10	
12/14/12	...	13″	10	
12/15/12	...	13″	10	
12/16/12	...	13″	10	
12/17/12	0.3	13″	10	
12/22/12	...	...	10	Frog killed.

Reaction to Induction Shock:

Gastrocnemii, direct application:

Right, 11 cm. negative; 10 cm. negative; 9½ cm. positive.

Left, 11 cm. negative; 10 cm. positive.

Work: Right, 119.2 gm. mil; left, 173.8 gm. mil.

FROG 14. WEIGHT 30 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
12/ 9/12	...	12″	10	Direct stimulation of
12/10/12	...	12″	10	right gastrocnemius.
12/11/12	...	12″	10	
12/12/12	...	12″	10	
12/13/12	...	12″	10	No symptoms.
12/14/12	...	12″	10	No symptoms.
12/15/12	...	12″	10	No symptoms.
12/16/12	...	12″	10	No symptoms.
12/17/12	0.35	12″	10	
12/22/12	...	...	....	Killed frog.

Reaction to Induction Shock:

Gastrocnemii, direct application:

Right at 9 cm. positive; at 10 cm. negative.

Left at 11 cm. positive

Work: Gastrocnemius, right, 125.2 gm. mil.; left, 169.7 gm. mil.

FROG 15. WEIGHT 32 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
12/ 9/12	...	12″	10	Direct stimulation of right gastrocnemius.
12/10/12	...	12″	10	
12/11/12	...	12″	10	
12/12/12	...	12″	10	
12/13/12	...	12″	10	Frog died; no result.

FROG 16. WEIGHT 27 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
12/ 9/12	...	12″	10	Direct stimulation of right gastrocnemius.
12/10/12	...	12″	10	
12/11/12	...	12″	10	
12/12/12	...	12″	10	
12/13/12	...	12″	10	
12/14/12	...	12″	10	
12/15/12	...	12″	10	
12/16/12	...	12″	10	
12/17/12	0.4	12″	10	No symptoms.
12/22/12	...	...	....	Killed frog.

Reaction to Induction Shock:

Gastrocnemii, direct application:

Right at 9 cm. positive; at 10 cm. negative.

Left at 12 cm. positive.

Work: Right gastrocnemius, 127; left, 178.4.

FROG 17. WEIGHT 28 GM.

Date	Amount of Lead, c.c.	Stimulation Amount of	Position of Secondary Coil, cm.	Notes
12/ 9/12	...	12″	10	Direct stimulation of right gastrocnemius.
12/10/12	...	12″	10	
12/11/12	...	12″	10	
12/12/12	...	12″	10	
12/13/12	...	12″	10	
12/14/12	...	12″	10	
12/15/12	...	12″	10	
12/16/12	...	12″	10	
12/17/12	0.45	12″	10	
12/18/12	...	12″	10	Slight stupor.
12/19/12	...	12″	10	Recovered.
12/22/12	...	...	....	Frog killed.

Reaction to induction shock and work practically the same as in Frog 16.

series (Frogs 3 and 4) recovered from doses of 0.25 c.c. and 0.5 c.c. of lead, respectively. Number 5 died with a dose of 0.75 c.c. The frogs in Series II (Frogs 6, 7 and 8) received, respectively, 0.5, 0.6 and 0.7 c.c. of lead. Number 6 recovered and Nos. 7 and 8 died from the effects of the lead. Thus 0.6 c.c. is the M.L.D. of neutral lead acetate for a 30-gm. frog, or 0.02 c.c. per gram.

FROG 18. WEIGHT 33 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
12/ 9/12	...	12″	10	Direct stimulation of right gastrocnemius.
12/10/12	...	12″	10	
12/11/12	...	12″	10	
12/12/12	...	12″	10	
12/13/12	...	12″	10	
12/14/12	...	12″	10	
12/15/12	...	12″	10	
12/16/12	...	12″	10	
12/17/12	0.48	12″	10	
12/18/12	...	12″	10	Progressive stupor.
12/19/12	...	12″	10	Progressive stupor.
12/20/12	...	12″	10	Progressive stupor.
12/21/12	...	...	10	Frog killed.

Reaction work practically the same as in Frog 16.

FROG 19. WEIGHT 31 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
12/ 9/12	...	12″	10	Direct stimulation of right gastrocnemius.
12/10/12	...	12″	10	
12/11/12	...	12″	10	
12/12/12	...	12″	10	
12/13/12	...	12″	10	
12/14/12	...	12″	10	
12/15/12	...	12″	10	
12/16/12	...	12″	10	
12/17/12	0.5	12″	10	
12/18/12	...	12″	10	Progressive stupor.
12/19/12	...	...	....	Frog killed.

Reaction to even strong induction slight, and work practically *nil.*

In Section C of Experiment Protocol, it is seen that 12 frogs were used. With these the direct method of stimulation prevailed throughout. This method consisted in the direct application of the electrodes at either

end of the gastrocnemius muscle. To obtain a suitable place for the electrodes, the muscle was denuded over an area of approximately 6 mm. square. This method was open to the objection that after varying lengths of time, the muscle underwent changes deleterious to the success of the experiments, as it afterward proved. Petechiae, induration and occasional sloughing occurred at the electrodal points. It is self-evident that the more serious change would disqualify the muscle, and presumably the slighter changes were without favorable influence.

FROG 20. WEIGHT 30 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
12/ 9/12	...	12″	10	Direct stimulation of right gastrocnemius.
12/10/12	...	12″	10	
12/11/12	...	12″	10	
12/12/12	...	12″	10	
12/13/12	...	12″	10	
12/14/12	...	12″	10	
12/15/12	...	12″	10	
12/16/12	...	12″	10	
12/17/12	0.5	12″	10	
12/18/12	...	12″	10	Marked stupor.
12/19/12	...	...	....	Frog killed.

Reaction to induction shock negative, even to strong current. Work practically *nil*.

D. DETERMINING THE RESULTS OF FATIGUE BY THE INDIRECT METHOD IN LEAD POISONED FROGS

FROG 21. WEIGHT 28 CM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
1/ 5/13	...	12″	8–9	Left gastrocnemius fatigued by indirect method. No symptoms at any time.
1/ 6/13	...	12″	8–9	
1/ 7/13	...	12″	8–9	
1/ 8/13	...	12″	8–9	
1/ 9/13	...	12″	8–9	
1/10/13	...	12″	8–9	
1/11/13	...	12″	8–9	
1/12/13	...	12″	8–9	
1/13/13	0.125	12″	8–9	
1/17/13	...	...	...	Frog killed.

Reaction to Induction Shock:
All muscles react well at 12 cm.
Work: Right gastrocnemius, 265.4 gm. mil.; left, 27.8 gm. mil.

Recourse to Section C shows considerable variance in the energy of the right and left gastrocnemii of Frog 10. As this animal had no lead at any time, we are forced to the conclusion that the diminution in the force of contractile power of the right or stimulated muscle is mostly the result of its damage during fatigue. This is made quite manifest when we consult Section D, Frog 24 (control); here the disparity in muscular power is so slight as to be irrelevant.

FROG 22. WEIGHT 28 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
1/ 5/13	...	15″	8–9	Left gastrocnemius fatigued by indirect method. No symptoms at any time.
1/ 6/13	...	12″	8–9	
1/ 7/13	...	15″	8–9	
1/ 8/13	...	15″	8–9	
1/ 9/13	...	15″	8–9	
1/10/13	...	15″	8–9	
1/11/13	...	15″	8–9	
1/12/13	...	15″	8–9	
1/13/13	0.175	15″	8–9	
1/17/13	...	...	...	Frog died.

FROG 23

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
2/ 5/13	...	13″	8–9	Left gastrocnemius fatigued by indirect method.
2/ 6/13	...	13″	8–9	
2/ 7/13	...	13″	8–9	
2/ 8/13	...	13″	8–9	
2/ 9/13	...	13″	8–9	
2/10/13	...	13″	8–9	
2/11/13	...	13″	8–9	
2/12/13	...	13″	8–9	
2/13/13	...	13″	8–9	
2/14/13	0.125	13″	8–9	
2/17/13	...	13″	8–9	
2/18/13	...	13″	8–9	
2/24/13	...	...	...	Frog killed.

For curve of work see chart (Fig. 2).
Work: Right gastrocnemius, 276.7 gm. mil; left, 13 gm. mil.

Although in this series the fatigued muscle in the lead-poisoned frog showed considerable diminution in energy, the qualitative difference is not decisive when compared with the control frog. The gastrocnemii of

Nos. 9, 11, 13, 14 and 16 show, respectively, 97.3, 107, 119.2, 125.2 and 127 gm. millimeters of work as against 132 gm. millimeters for control Frog. 10. Since Frog 9 was not killed, post mortem changes can partially account for its decrease, particularly when the opposite leg showed a corresponding change.

FROG 24. NORMAL CONTROL. WEIGHT 32 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
2/ 5/13	...	13″	8–9	Left gastrocnemius
2/ 6/13	...	13″	8–9	stimulated by indirect
2/ 7/13	...	13″	8–9	method.
2/ 8/13	...	13″	8–9	No symptoms.
2/ 9/13	...	13″	8–9	No symptoms.
2/10/13	...	13″	8–9	No symptoms.
2/11/13	...	13″	8–9	No symptoms.
2/12/13	...	13″	8–9	No symptoms.
2/13/13	...	13″	8–9	No symptoms.
2/14/13	...	13″	8–9	No symptoms.
2/17/13	...	13″	8–9	No symptoms.
2/18/13	...	13″	8–9	No symptoms.
2/24/12	...	...	...	Frog killed.

For results, see curve and plot (Fig. 3).
Work: Right gastrocnemius, 287 gm. mil.; left, 274.5 gm. mil.

FROG 25. WEIGHT 33 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
2/ 6/13	...	13″	8–9	Left gastrocnemius
2/ 7/13	...	13″	8–9	stimulated by indirect
2/ 8/13	...	13″	8–9	method.
2/ 9/13	...	13″	8–9	
2/12/13	...	13″	8–9	No symptoms.
2/13/13	...	13″	8–9	No symptoms.
2/14/13	...	13″	8–9	No symptoms.
2/15/13	...	13″	8–9	No symptoms.
2/16/13	0.175	13″	8–9	No symptoms.
2/20/13	...	...	...	Frog killed.

Reaction to Induction Shock:
Both gastrocnemii react well at 12 cm.
Work: Right gastrocnemius, 270.5 gm. mil.; left, 39.3 gm. mil.

An analysis of Section D gives an entirely different view. Here most of the results are clear and decisive. There can be no question that the disparity in the contractile power of the muscles of Frogs 21, 23, 25 and 26 is not due to the lead, except as the fatigue facilitates the pathological changes which characterize it.

By reference to the plotted curve (Fig. 1) representing the experiment with Frog 23, it is obvious that its right gastrocnemius was able to do 276.7 gm. millimeters of work. The left, or fatigued gastrocnemius, was able to perform but a scant 13 gm. millimeters of work. It is self-evident that the former is able to do 21.24 times the work done by the latter.

FROG 26. WEIGHT 31 GM.

Date	Amount of Lead, c.c.	Stimulation Amount of	Position of Secondary Coil, cm.	Notes
2/ 7/13	...	14″	8–9	Left gastrocnemius fatigued by indirect method.
2/ 8/13	...	14″	8–9	
2/ 9/13	...	14″	8–9	
2/10/13	...	14″	8–9	
2/11/13	...	14″	8–9	
2/12/13	...	14″	8–9	
2/13/13	...	14″	8–9	
2/14/13	...	14″	8–9	
2/15/13	0.2	14″	8–9	Very slight reflex diminution.
2/16/13	...	14″	8–9	Frog recovered.
2/21/13	...	...	...	Frog killed.

Reaction to Induction Shock:
Both gastrocnemii react well at 12 cm.
Work: Right gastrocnemius, 221.7 gm. mil.; left, 17.8 gm. mil.

FROG 27. WEIGHT 31 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
2/18/13	...	12″	8–9	Left gastrocnemius fatigued by indirect method.
2/19/13	...	12″	8–9	
2/21/13	...	12″	8–9	
2/22/13	...	12″	8–9	
2/23/13	...	12″	8–9	
2/25/13	...	12″	8–9	
2/26/13	...	12″	8–9	
2/27/13	...	12″	8–9	
2/28/13	0.225	12″	8–9	
3/ 2/13	...	12″	8–9	Slight decrease in reflexes and stupor.
3/ 4/13	...	12″	8–9	Frog killed.

Reaction to Induction Shock:
Both react well at 12 cm.
Work: Right gastrocnemius, 245.3 gm. mil.; left gastrocnemius, 17.9 gm. mil.

In order to eliminate the effect of the stimulation and lead separately, a normal frog of the same weight as No. 23 was given the same amount

of stimulation without the lead. This is Frog 24 (Fig. 2). By calculation it is seen that the right gastrocnemius has 287 gm. millimeters of work, while the left or fatigued gastrocnemius has 274.5 gm. millimeters. This leaves a difference of 12.5 gm. millimeters to account for the effect of fatigue in a normal frog, and 10.3 gm. millimeters for the effect of the lead. These are insignificant differences, particularly the 10.3 gm. millimeters which could be physiologic in character.

FROG 28. WEIGHT 30 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
2/16/13	...	13″	8–9	Left gastrocnemius fatigued by indirect method.
2/17/13	...	13″	8–9	
2/18/13	...	13″	8–9	
2/19/13	...	13″	8–9	
2/20/13	...	13″	8–9	
2/21/13	...	13″	8–9	
2/24/13	...	13″	8–9	
2/25/13	...	13″	8–9	
2/26/13	0.25	13″	8–9	
3/ 2/13	...	13″	8–9	Frog killed.

Reaction to Induction Shock:
Both gastrocnemii react well at 12 cm.
Work: Right gastrocnemius, 195.6 gm. mil.; left, 19.8 gm. mil.

FROG 29. WEIGHT 33 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
3/ 3/13	...	12″	8–9	Left gastrocnemius fatigued by indirect method.
3/ 4/13	...	12″	8–9	
3/ 5/13	...	12″	8–9	
3/ 6/13	...	12″	8–9	
3/ 7/13	...	12″	8–9	
3/ 8/13	...	12″	8–9	
3/ 9/13	...	12″	8–9	
3/10/13	...	12″	8–9	
3/11/13	...	12″	8–9	
3/12/13	0.3	12″	8–9	Slight stupor.
3/14/13	...	12″	8–9	Recovered fully.
3/15/13	...	12″	8–9	
3/16/13	...	12″	8–9	
3/16/13	...	12″	8–9	
3/20/13	...	...	...	Frog killed.

Reaction to Induction Shock:
Both gastrocnemii react well at 12 cm.
Work: Right gastrocnemius, 203.6 gm. mil.; left, 21.7 gm. mil.

FROG 30. WEIGHT 32 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
3/ 8/13	...	12"	8–9	Left gastrocnemius fatigued by indirect method.
3/ 9/13	...	12"	8–9	
3/10/13	...	12"	8–9	
3/11/13	...	12"	8–9	
3/12/13	...	12"	8–9	
3/13/13	...	12"	8–9	
3/14/13	...	12"	8–9	
3/15/13	...	12"	8–9	
3/16/13	...	12"	8–9	
3/17/13	0.35	12"	8–9	Well developed stupor followed Pb. injection.
3/20/13	...	12"	8–9	Frog recovered only partially; at times fairly irritable; at other times listless.
3/21/13	...	...	...	Frog killed.

Reaction to Induction Shock:

Direct application:

Right at 12 negative; at 11.5 positive.

Left at 11 negative; at 10.5 positive.

Work: Right gastrocnemius, 183; left, 21.2.

FROG 31. WEIGHT 29 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
3/15/13	...	12"	8–9	Left gastrocnemius fatigued by indirect method.
3/16/13	...	12"	8–9	
3/17/13	...	12"	8–9	
3/18/13	...	12"	8–9	
3/19/13	...	12"	8–9	
3/20/13	...	12"	8–9	
3/21/13	...	12"	8–9	
3/22/13	...	12"	8–9	
3/23/13	...	12"	8–9	
3/24/13	0.45	12"	8–9	Marked stupor and reflex diminution following Pb. injection. Recovery only slight, and then seemed to grow progressively worse.
3/28/13	...	...	...	Frog killed.

Reaction to Induction Shock:

Direct application:

Right gastrocnemius at 10 negative; at 9 positive.

Left gastrocnemius at 8 negative, at 7 positive.

Work: Right gastrocnemius, 141.3 gm. mil.; left, 15.4 gm. mil.

Frogs 29, 30, 31 and 32 show the effect of increasing dosage by producing stupor and diminution of reflexes. The confusion in the results of the quantitative work is also noted. Although the fatigued muscle shows a very marked decrease in energy, the unfatigued muscle is also affected so markedly that one is at a loss to know how much to attribute to fatigue and how much to the lead itself. This confusion is averted in the frogs referred to above.

In this work, two methods of fatigue were used. First, a direct application of the electrodes to the muscles, and second, an electrical irritation of the skin which produced a muscular contraction resulting from the frog's attempt to get away from the irritation. This was accomplished by an apparatus which I devised for the purpose, the details of which appear later.

FROG 32. WEIGHT 32 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
3/20/13	...	12″	8–9	Left gastrocnemius fatigued by indirect method.
3/21/13	...	12″	8–9	
3/22/13	...	12″	8–9	
3/23/13	...	12″	8–9	
3/24/13	...	12″	8–9	
3/25/13	...	12″	8–9	
3/27/13	...	12″	8–9	
3/28/13	...	12″	8–9	
3/29/13	...	12″	8–9	
3/30/13	0.53	12″	8–9	
3/31/13	...	...	...	Marked stupor which grew progressively worse. Reflexes also diminished markedly. Frog will probably not recover.
4/3 /13	...	...	...	Frog killed.

Reaction to Induction Shock:

Direct application:

Right gastrocnemius at 7 negative; at 6 positive.

Left gastrocnemius at 4 negative; at 3 positive.

Work: Right gastrocnemius, 75.4 gm. mil.; left, practically *nil.*

The first method was fairly successful in the gross, but was a complete failure when accurate methods were used. This is clearly shown by the experiments in Section C of the Protocol of Experiments. The reasons for the inefficiency of this method have already been explained. The abandonment of this method resulted in the adoption of another, which makes use of an apparatus which the subjoined diagram will render obvious (Fig. 3).

Tension is put on the left leg of the frog by anchoring it to the binding post P. A piece of twine is used which is about an inch long. It is not well to have it longer, as too much freedom of motion obtains. Some suitable electrode is placed adjacent to the tendon of the gastrocnemius at A, the height of the electrode being regulated by a piece of tin-foil which supports it at T F.

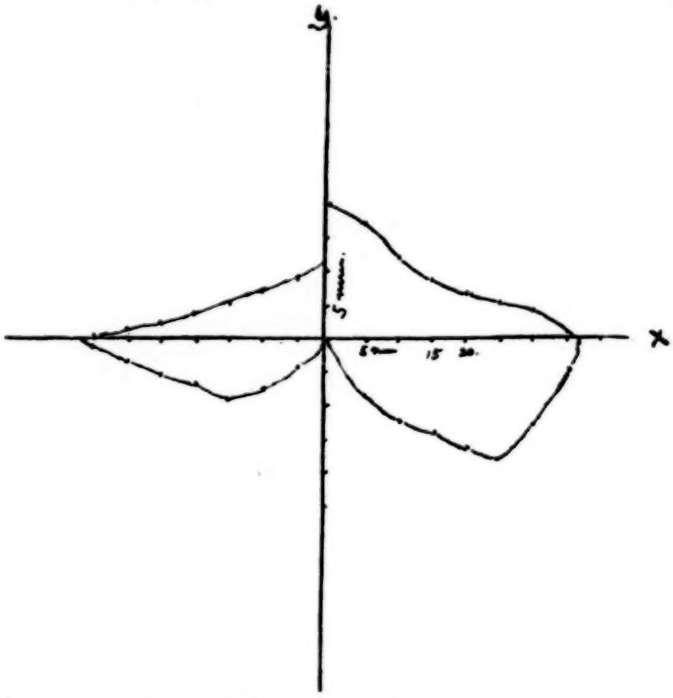

Fig. 1.—Explanation of Plotted Curves. (Frog 23.) The curves represent the type of results derived from the indirect form of stimulation in a lead frog. The abscissa and ordinate are ruled off in spaces of 5 mm. each. To the right of the ordinate Y is represented the curve of lift and curve of work of the right gastrocnemius. The former is above the abscissa, and the latter below. To the left of the ordinate is represented the curves of lift and work of the left gastrocnemius. The disparity shown between the two curves of work and lift is not absolute, as those for the left leg are magnified ten times.

One electrode is fastened to the front leg of the frog by a curved copper wire, and the current is closed by the contact of the electrode with the tendon of the gastrocnemius. The resulting irritation causes a sudden contraction of the leg and thigh muscles, which break the circuit by the withdrawal of the leg from the electrode. The gastrocnemius is invariably contracted by this movement, as can be evidenced by palpation.

The break in the circuit almost instantly permits the leg to drift back on the point of the electrode when the contraction is repeated. In a normal 25-gm. frog, this rate may run from three to four per second, but it is not long before the rate becomes rapidly decreased to one or two per second.

It is entirely self-evident that the greatest advantage accruing from this simple device is the one which makes use of fatigue of muscles by mechanical means, even though the induction coil is used as the exciting factor.

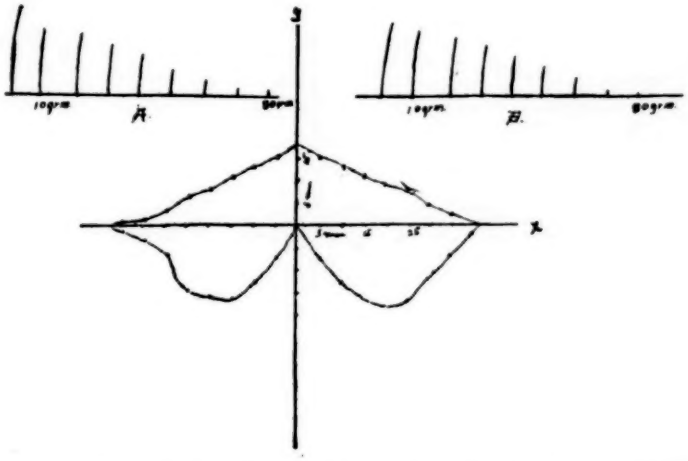

Fig. 2.—Explanation of Plotted Curve. (Frog 24.) The curve represents the results obtained by the indirect form of stimulation in a control frog which had received no lead. The curves to the right of the abscissa represent the right leg, and those to the left, the left leg. There is no magnification of any curve on either side. Tracings A and B represent the excursion of the left and right gastrocnemii muscles, respectively, under stimulus of a weak induction shock, and weighted with loads of from 10 to 80 grams.

This method besides being admirably adapted to our purpose, in that it imitates fairly perfectly the actual contraction of human muscles in doing work, requires no additional apparatus. The pure electrical form of stimulation, even when perfect, is open to the objection that it does not parallel closely the mechanical form used by man in his labor. Its applicability to our proposition is well illustrated by the fact that muscles of a normal frog do not lose perceptibly in power when stimulated in this way, when sufficient time is given for recovery from the fatigue induced.

The experiments showed the importance of the administration of a subphysiological dose of lead. Good results were almost always obtained when the doses were not so large as to produce stupor and marked dimin-

ution of reflexes to mechanical and electrical stimulation. In case this caution is not observed, the non-stimulated as well as the stimulated muscles show loss of power.

As in all work of this nature, a terminal recovery interval should be observed. In order to determine whether the loss of power in a muscle is permanent, the effects of ordinary fatigue should be permitted to disappear. In muscles fatigued only once a day, forty-eight to seventy-two hours suffice admirably for such restoration. Possibly less time would do, but a generous margin was left so it would not be possible to account for the loss of power in the lead frog from the effects of the stimulation.

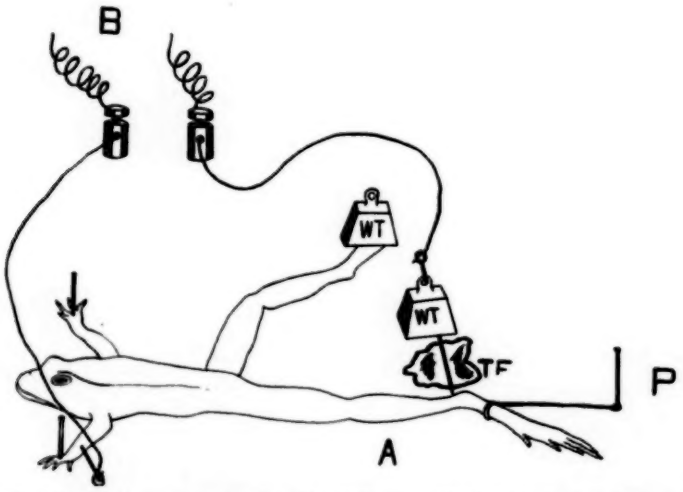

Fig. 3.—Diagram representing the indirect method of inducing fatigue of muscle. For explanation see text.

SUMMARY

1. That the quantitative differences between the amount of work done by the fatigued and non-fatigued leg in a lead-poisoned frog is not conclusive when the direct application of the electric current is used for muscle fatigue.

2. No conclusive quantitative differences are observed where large enough doses of the metal are given to produce stupor and marked diminution of reflexes.

3. That these experiments, as worked out by the indirect method of fatigue production, are conclusive evidence of the validity of Edinger's

contention, viz., that lead in itself has no predilection for any group of muscles except as that choice is made possible by their over-use. Fatigue is, therefore, the main factor in the localization of lead palsies.

The Harvard inductorium, manufactured by the Harvard Apparatus Co., was used in all the experiments. The battery was a single Columbia dry cell.

Acknowledgement is made to the Department of Physiology, to Dr. Lombard, Dr. Cope and Mr. F. T. Munson for apparatus loaned me; and to Dr. Warthin for the suggestion of the problem and his control of the investigation.

ON THE REINSPIRATION OF EXPIRED AIR*

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I desire to record a phenomenon and to discuss its significance.

The phenomenon is, the immediate reinspiration of a portion of our expired air. This occurs quite commonly — so commonly, in fact, that it is an accompaniment of respiration during the major part of the lives of many people, and during a large part of the lives of practically all.

The observation of this phenomenon is not new. Lehmann[1] and Heymann[2] have each reported a small group of experiments, in which they determined the carbon dioxid of the inspired air, compared this with the carbon dioxid of the surrounding air, and from the difference computed the proportion of the breath which was reinspired. The proportion varied greatly. It was sometimes more than 6 per cent.; it dropped to zero in the open air and in a breeze of 3 meters per second.

A few years ago this subject attracted my attention in connection with certain studies of ventilation. The experiments of Lehmann and Heymann demonstrated little except that reinspiration may and does occur. It seemed desirable to carry the observations further. As opportunity arose this has been done, and an attempt has been made to determine some of the factors controlling this phenomenon. The work has included the analysis of about 900 samples of inspired air.

METHODS

In order to find what proportion of the expired air re-enters the respiratory tract with the succeeding inspiration, it is necessary to collect samples of the inspired air as it enters the nasal passages and subject them to analysis. The only difficulty in collecting the samples arises through the possibility of including a portion of the expired air as it *leaves* the nasal passages. This is likely to occur if the taking of the sample is not accurately timed to the inspiratory period; collection must begin after inspiration is established and must end before expiration has begun.

Experiments such as these are more readily carried out on oneself than on a second person, because of the easier identification of the

* Submitted for publication July 15, 1913.

1. Lehmann: Der Kohlensäuregehalt der Inspirationsluft im Freien und im Zimmer, Arch. f. Hyg., 1899, xxxiv, 315.

2. Heymann: Ueber den Einfluss wieder eingeathmeter Expirationsluft auf die Kohlensäure-Abgabe, Ztschr. f. Hyg., 1905, xlix, 388.

respiratory periods. With a little practice one may become perfectly conscious of the beginning and end of inspiration; and with a little more practice may learn to bring the inlet tube of a bellows into the nasal orifice at the proper moment and to remove it at the proper moment, using one hand meanwhile to manipulate the bellows. By arranging for an air current that will immediately carry away all of the expired air, a series of controls may be run that will show clearly when the technic is mastered. The observations herewith recorded were made by the author on himself. Those made by the experimenters above referred to were made on a second person.

After various trials of more or less complicated apparatus, a very simple plan of collecting samples was adopted. The ordinary Paquelin cautery bulb was found to answer very well for this purpose after a little alteration. The only necessary alterations are a long rubber tube with

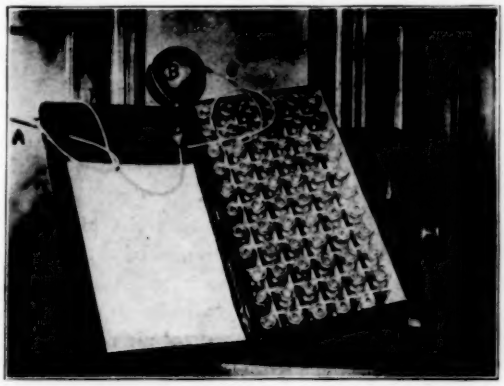

Fig. 1.—Apparatus used in collecting samples of air. *A*, intake tube; *B*, bellows; *B'*, the elastic bag: *O*, outlet tube.

a glass tip attached to the bellows intake, and a pinch-cock applied to the outlet tube from the elastic bag. A somewhat larger and heavier bag than that ordinarily supplied with the cautery was used, but the arrangement was essentially the same. The accompanying photograph (Fig. 1) shows the apparatus used, and the case for collecting and carrying samples and records. *A* is the intake tube. *B* is the bellows, *B'* the elastic bag and *O* the outlet tube.

After inspiration is well established the glass inlet tube is brought just within the nasal orifice — or between the parted lips during mouth breathing — and the bellows given two or three quick compressions. The inlet tube is removed during expiration and is again brought into place

during the succeeding inspiration. This is repeated during eight or ten breaths, or until about 1,000 cubic centimeters of air have been collected in the bag. The outlet tube is then thrust to the bottom of a two-ounce bottle and the air run through it by releasing the pinch-cock. This leaves the sample of air in the bottle. On withdrawal of the tube a waxed glass stopper is inserted and the seal made perfect. If the bottle is clean and dry there will be no change in the air it contains for a fortnight or more. The samples are then transferred under a saturated solution of sodium chlorid to a Petterson-Palmquist apparatus and analyzed for carbon dioxid. The details of the various steps, the necessary precautions and the accuracy of the method have been previously discussed.[3]

At the time the samples of inspired air are collected, samples of the surrounding air must also be taken. The amount of immediate reinspiration is measured by the difference in the carbon dioxid content of these two. In the accompanying charts this difference is shown directly, and the proportion of CO_2 in the air is expressed in ten-thousandths of the whole volume. In the text, reinspiration is referred to in terms of per cent.; that is, the proportion of expired air which is mixed with the inspired air and which is therefore reinhaled after it has been once expelled. It may be assumed that for every 4.5 per 10,000 difference between the CO_2 of the inspired air and of the surrounding air, 1 per cent. of the expired air is being reinspired. This is derived by a very simple computation, based on the fact that the expired air contains about 450 volumes of CO_2 in 10,000 volumes of air. It will of course vary a little from this figure, which is an average, but the variation will be relatively small and will affect the computation only slightly.

It should be remembered that the normal air contains 3.5 to 4 parts of CO_2 per 10,000. All above this is contamination, the result of respiration, burning lights, or other chemical processes. In the majority of instances all CO_2 above 4 per 10,000 represents respiratory contamination; and in a broad sense all CO_2 above 4 per 10,000 in the inspired air generally represents reinspiration. But for our present purpose we shall consider only the CO_2 which is in excess of the amount contained in the general surrounding air; for it is this portion only which represents that strictly local contamination which leads to the immediate reinspiration of our exhalations now under discussion.

RESULTS

It was soon noticed that, under apparently fixed conditions, repeated observations of the inspired air would always show considerable variation

3. Crowder: A Study of the Ventilation of Sleeping Cars, THE ARCHIVES INT. MED., 1911, vii, 85.

in the CO_2 content. All experiments were therefore carried out with serial tests, including from 4 to 24 successive samples, in order to arrive at averages. The individual observations of such series can be made at about one minute intervals when one is standing or sitting. They will fall a little farther apart when lying down, or under any circumstances which occasion interference with the easy manipulation of the apparatus and the records.

It proved desirable to alter the surrounding conditions, especially the amount of ventilation, at the same time and place, or to induce artificial air currents, and observe the effects on the phenomenon under investigation by running parallel series of tests. The effect of changes of position, body motion, different types of breathing, different temperatures and different degrees of contamination of the surrounding air were also investigated; and finally, the question of whether or not reinspiration takes place in such half-sheltered places as the sleeping-porch and in the open air. The results will follow in order. Unless otherwise specified, nasal breathing is referred to.

THE AIR ABOUT THE FACE

If the conditions are such that reinspiration can take place the air about the face will necessarily be found to contain more CO_2 than the surrounding air. It is on the fact that the expired air is not immediately removed or disseminated that reinspiration depends. That it remains about the face for an appreciable interval, is easily demonstrated. This is illustrated in Figure 2.

The heavy horizontal line in this, as in succeeding charts, represents the CO_2 in the general air of the room. It was constant to within half a point of 4.5 per 10,000. This half a point in 10,000, or 1 in 20,000, may be considered as about the maximum necessary error of the determinations. The series of samples represented by the upper curve, marked *A*, were taken close to the nose while holding the breath at the end of normal expiration; they contain an average of 3.8 per cent. of expired air. Those represented by the lower curve, marked *B*, were taken at the same place while holding the breath at the end of normal inspiration; they contain an average of 0.9 per cent. of expired air. The time occupied in collecting each of these samples was about five seconds. Those represented by the middle curve, marked *C*, were taken from within the nasal orifice during inspiration; they, therefore, show the contamination of the inspired air, which averaged 7.5 more CO_2 per 10,000 than was contained in the air of the room. This excess of CO_2 represents 1.7 per cent. of expired air; we therefore have for this series 1.7 per cent. of reinspiration. The average for each series is shown by the short horizontal line at the right. This experiment was carried out while sitting in

a well-ventilated room of 3,000 cubic feet capacity, having three windows and three doors. The temperature was 73 F.

A little variation of the last experiment will show that this local contamination reaches a considerable distance below the face, and that it decreases with increasing distance. Figure 3 illustrates some of the results with such a variation. At *A* is shown a series of samples taken close to the body and 6 to 8 inches below the nose during expiration;

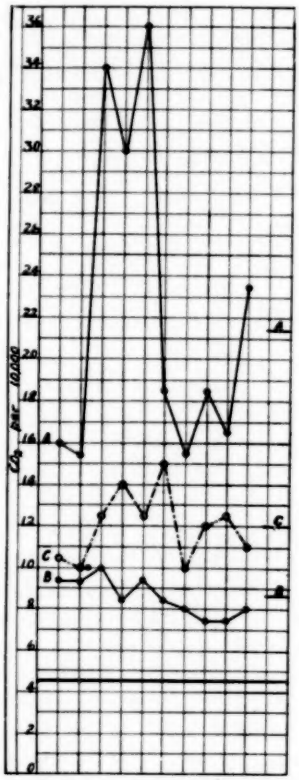

Fig. 2.—(Exper. 22). Showing contamination of the air about the face while holding the breath after expiration (*A*), after inspiration (*B*), and of the inspired air (*C*).

they contain an average of 4.6 per cent. of expired air. At *B* is shown a series taken 12 to 15 inches below the nose during expiration, and they contain 2.8 per cent. of expired air. At *C* the samples were taken 6 to 8 inches below the nose during inspiration, and contain 0.7 per cent. of expired air. At *D* the samples were taken 12 to 15 inches below the nose

during inspiration, and the contamination amounts to only 0.1 per cent. of expired air. These tests were made in the same room as the above, when there was a measured air-supply in excess of 15,000 cubic feet per hour entering through an open transom. The temperature was 66 F.

The conditions noted in Figures 2 and 3 are fundamental to our investigation. The contamination may be traced further; it tends to disappear rapidly, both in the time and space relation. The general facts are not particularly new or strange. They may be roughly determined by any one who will watch the course of smoke blown through the nostrils.

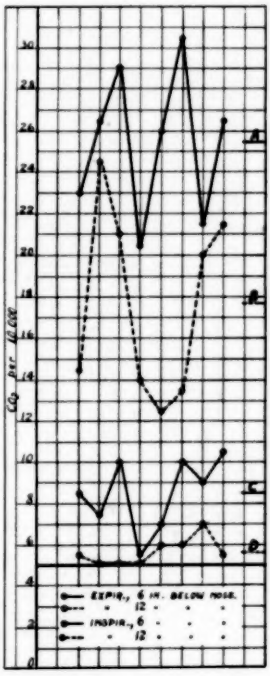

Fig. 3.—(Exps. 8 and 9). Showing contamination of the air 6 to 8 inches and 12 to 15 inches below the nose during expiration (*A* and *B*), and at the same places during inspiration (*C* and *D*).

THE EFFECT OF TEMPERATURE

It has been sometimes stated before scientific societies that when the surrounding air is cool — below 60 F. or thereabouts — the expired air will rise out of the breathing zone on account of its lower specific gravity, and reinspiration will not take place. The results shown in the last chart would seem to cast a doubt on the theoretical correctness of this

view. Those making the statement have failed to consider the downward propulsion of the expired air from the nares, that it takes on a cone-shaped expansion, a part of which lies quite close to the body, and that convection currents tend to carry this part upward over the face. Inspiration succeeds expiration almost immediately; any upward current would therefore have to be very rapid in order to carry this air away before the latter process begins. Convection currents caused by the heat of the body, instead of being rapid, are just the opposite.

That reinspiration undoubtedly does take place at temperatures much below 60 F. will be seen from the two series of observations illustrated in Figure 4. That at the left was made in a large room of 16,000 cubic feet, with windows on three sides. It had a temperature of 50 F., and

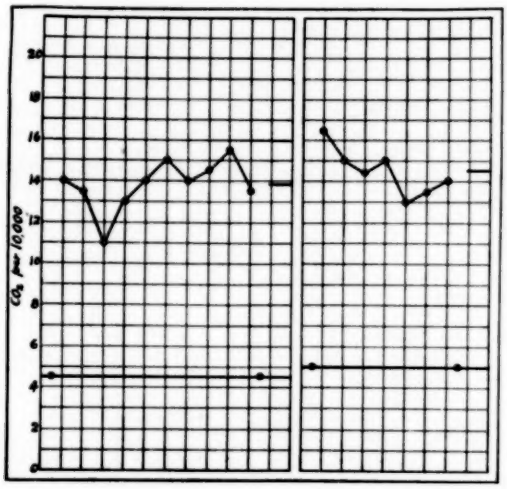

Fig. 4.—(Exps. 24 and 27.) Showing the inspired air while standing in a room of 16,000 cubic feet at 50 F. (at the left), and in a room of 1,500 cubic feet at 43 F. (at the right).

the reinspiration averaged 2.1 per cent. That at the right was made in a small room of 1,500 cubic feet. The temperature was 43 F. and the reinspiration also averaged 2.1 per cent.

If a low temperature has any effect it tends to increase reinspiration. Within certain limits I believe that it does this, though I am not prepared to show that it has any constantly appreciable effect. Figure 5 shows an attempt to make the comparison in a cold and in a warm air with otherwise uniform conditions. The experiment was carried out in a small bedroom of some 1,200 cubic feet capacity. The windows and doors were closed. All samples were taken while standing perfectly free,

about the middle of the room. Each series runs through about half an hour's time. For that shown on the left the temperature was 34 F. and the reinspiration amounts to 2.3 per cent. For that shown at the right the temperature was 70 F. and the reinspiration amounts to 2 per cent. The former was taken late at night, the latter late the next morning. The changing CO_2 in the general air of the room may be accounted for by the presence of the experimenter; and the difference in the CO_2 of this air for the two series by pure air entering from without through the window crevices in the first, whereas in the last the currents were reversed and air was entering from the hallway after being already slightly contaminated. In each instance the room had been unoccupied before the beginning of the experiment.

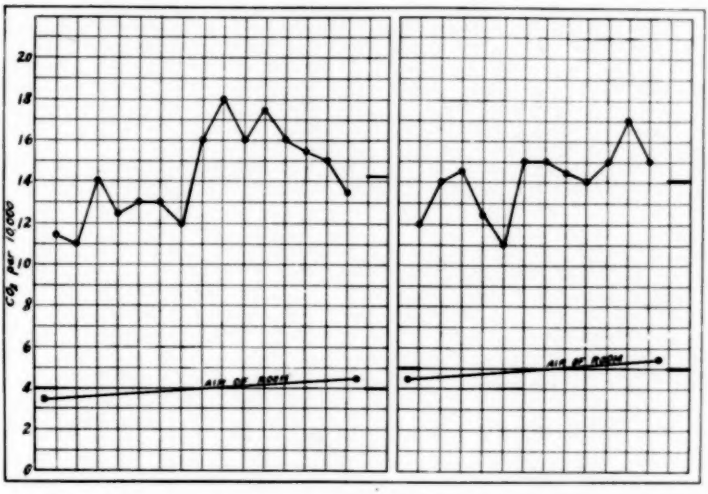

Fig. 5.—(Exp. 23). Showing the inspired air in a room with a temperature of 34 F. (on the left), and in the same room with a temperature of 70 F. (on the right), all other conditions remaining essentially the same.

THE EFFECT OF VENTILATION CURRENTS

It is reasonable to suppose that the greater the volume of air supplied to a room the less evident will be the phenomenon of reinspiration, because of the greater motion imparted to the air of the confined space. In a measure, this supposition is correct; but it does not follow that a large air-supply to a room will entirely prevent the immediate reinspiration of expired air by the occupants. There are a number of factors determining the limits of air-supply which will be found of too much importance to permit of a sufficient ventilation to control the matter entirely, or even to limit it in a very marked degree.

The results of an experiment carried out in a small bedroom of about 1,000 cubic feet, and also at the low temperature of 43 F., are illustrated in Figure 6. The room has one window and two doors. A strong wind was blowing without. The series shown at the left was taken with closed doors and window; in that at the right the window was raised so as to give one square foot of opening, and admitted air at the rate of 16,500 cubic feet per hour — enough to accomplish in excess of sixteen complete changes each hour. In the first, the reinspiration amounts to 1.9 per cent.; in the second it fell to only 1.4 per cent. Most of the samples of air were taken while standing, a few while sitting on the edge of the bed, which was about 6 feet from the window. It is probable that there is a slight error in determining the CO_2 in the air of the room for the

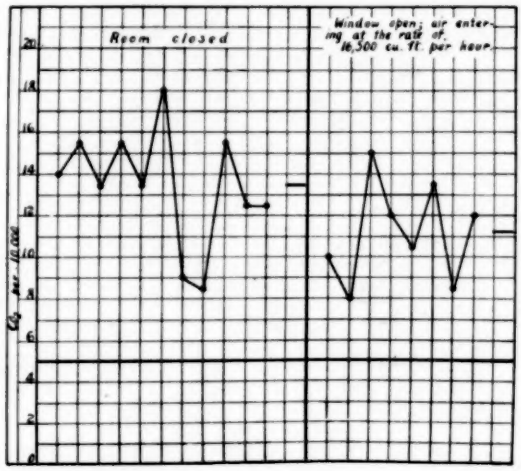

Fig. 6.—(Exp. 4). Showing the inspired air in a room with a small air supply and in the same room with a large air supply.

second series, and that the base line should be dropped to 4, which would make the difference between the two groups still less striking.

The difference produced by a large air-supply, or even by a moderate one, is, in many instances, more marked than in the above experiment. When one sits or stands directly between the inlet and the outlet, and the air-supply is large, the proportion of the breath which is reinspired may drop to nearly nothing. Two experiments made under these conditions in a room of 3,000 cubic feet with a temperature of 70 F. are shown in Figure 7. In each instance the air-supply came in through a door from the adjacent hallway and left through a window diagonally opposite. It was measured at the exit. The samples of inspired air were taken while

sitting directly in the line between door and window, and twice as far from the former as from the latter. In the curve marked *A* the air-supply was at the rate of 28,000 cubic feet per hour; in the curve marked *B* it was at the rate of 63,000 cubic feet per hour. The average reinspiration is 1.1 per cent. for *A*, and 0.6 per cent. for *B*. The base line representing the CO_2 in the general air of the room was not the same in these two instances, but in the chart the curves are adjusted to a common base of 5, in order to make a clear and accurate comparison.

On another occasion the same room was found to be receiving 324,000 cubic feet of air per hour through the open door. This was leaving through the open window as before. It was possible in this instance to measure by the anemometer the air current in the position occupied for

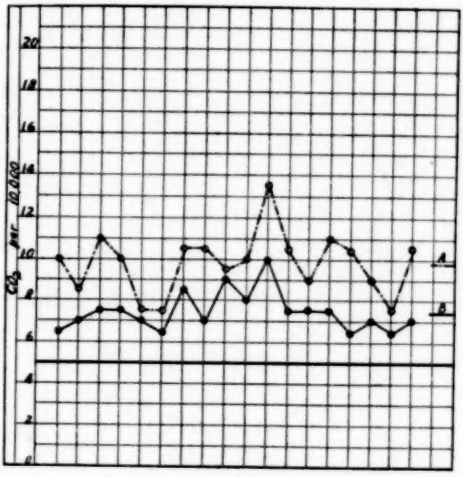

Fig. 7.—(Exps. 18 and 21). Showing the inspired air while sitting directly between inlet and outlet of a room of 3,000 cubic feet, ventilated by 28,000 cubic feet of air per hour (*A*), and by 63,000 cubic feet per hour (*B*).

the tests. This was found to be about 120 feet per minute. The negative results of the reinspiration test are shown in the curve marked *A* in Figure 8. But on moving about 6 feet out of the direct line between the door and the window the result was changed to a reinspiration of 0.6 per cent., as can be seen in the curve marked *B* in the same chart. In this latter position the anemometer moved irregularly, sometimes forward and sometimes backward. The amount of air being supplied during this experiment is of course much larger than can ordinarily be used to ventilate a room of this size, whatever the method of ventilation employed.

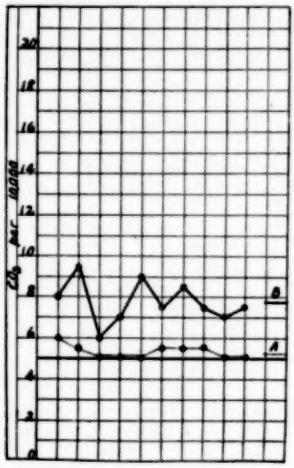

Fig. 8.—(Exper. 20). Showing the absence of reinspiration while sitting directly between inlet and outlet of a room of 3,000 cubic feet, ventilated by 324,000 cubic feet of air per hour (*A*), and its presence when sitting 6 feet out of the direct line (*B*).

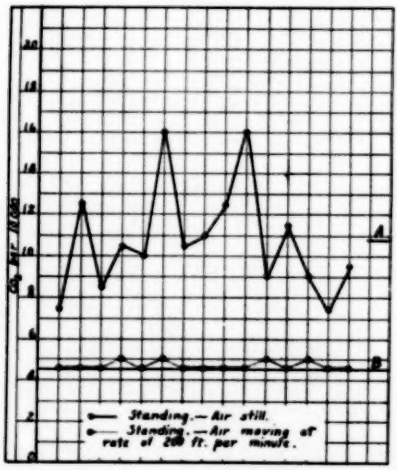

Fig. 9.—(Exper. 12). Showing that there is no reinspiration when facing a breeze of 200 feet per minute (*B*), contrasted with 1.4 per cent. reinspiration when the air is relatively still (*A*).

By the employment of properly directed artificial currents it is quite easy to prevent reinspiration entirely. This may be readily accomplished by means of an electric fan, provided the face is free to receive the breeze. If there is obstruction to the free flow of the current of air, the results may be quite different, as will be demonstrated later. Figure 9 shows very well what happens in a fan current moving at the rate of 200 feet per minute when there is no obstruction (curve *B*), and also what happens in the same place when the fan is shut off (curve *A*). Such an experiment also serves well as a control of the technic, which was identical for the two series. The room in which it was made contains 2,500 cubic feet and had a temperature of 68 F.

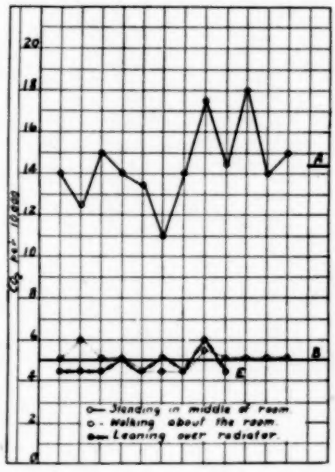

Fig. 10.—(Exp. 10). Showing no reinspiration when walking about the room (*B*), or when leaning over a radiator (*E*), contrasted with 2.1 per cent. when standing still (*A*).

The same result may be obtained by walking about the room, thus creating one's own current of some 200 to 300 feet per minute, and leaving behind at each step the expired breath. The walking may be confined to a very small circle without any change in the results. It is equally effective to stand with the head above a radiator, which, when well heated, will cause an upward convection current of some 200 feet per minute. Figure 10 illustrates these statements very well, and shows that 2.1 per cent. of the expired air was rebreathed when standing still. This experiment was made in the same room as the foregoing, with closed windows and a temperature of 63 F.

Results confirming those above noted are shown in Figure 11. When this experiment was made, the room was receiving 28,000 cubic feet of air per hour from an open window and the temperature was 66 F. On account of the large inflow of cool air, the air near the floor contained only 4 CO_2 per 10,000, while it had 4.5 at a height of 5 feet above the floor. The same difference is detected in curves *B* and *C*, the former of which represents samples of the inspired air taken in the upward current over the radiator, and the latter those taken while walking about the room. When standing quietly in the middle of the room the reinspiration was 1.2 per cent., as shown in the curve *A*.

In connection with the avoidance of reinspiration by induced air currents, the interesting observation has been made that when the back

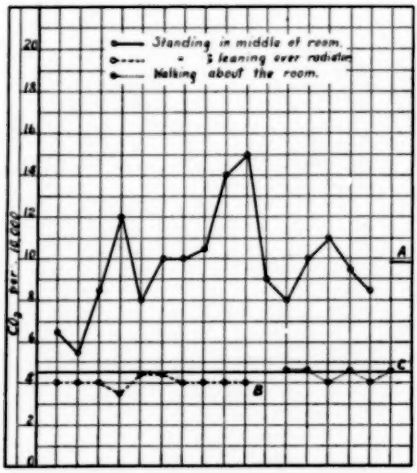

Fig. 11.—(Exp. 6). Showing no reinspiration when walking about the room (*C*), or when leaning over a radiator (*B*), contrasted with 1.2 per cent. when standing still (*A*). The room was receiving 28,000 cubic feet of air per hour from an open window.

is turned to the breeze a little of the expired air is often reinhaled in spite of the current. This is interpreted to mean that the eddies formed in front of the face prevent an immediate removal of the expired air. Two experiments made while standing in a narrow hallway with a very regular flow of air, and which illustrate this, are shown in Figure 12. In that shown at the left the current was just perceptible, presumably about 150 feet per minute; in that at the right the current was 300 feet per minute. The samples in each series were taken alternately, one while facing toward, then one while facing away from, the air current.

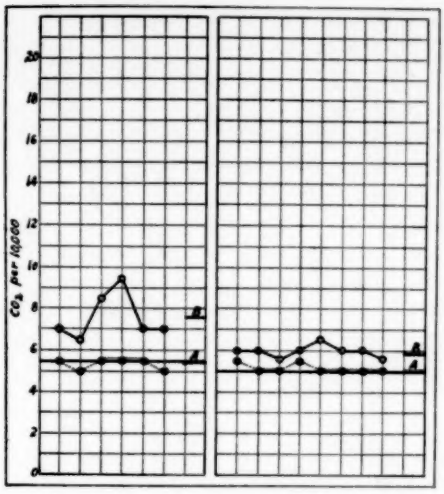

Fig. 12.—(Exps. 3 and 19). Showing that air currents of small velocity do not entirely prevent reinspiration when directed from behind (*B*), but do when directed from the front (*A*).

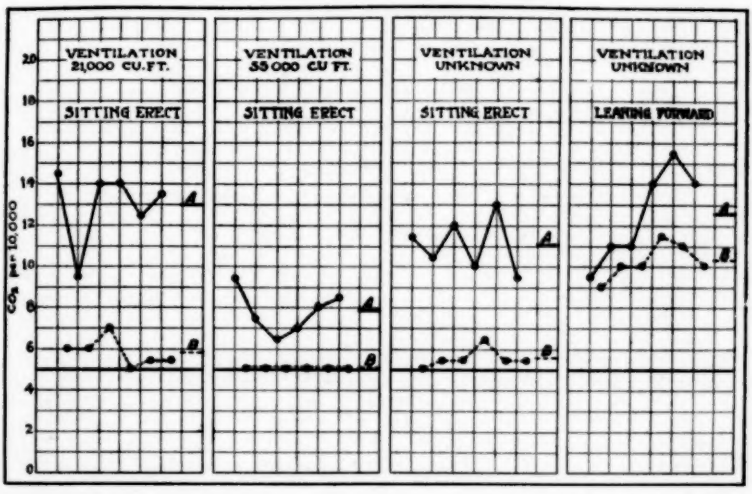

Fig. 13.—(Exper. 2). Showing that there is practically no reinspiration with mouth breathing unless the expired current is directed downward, as in *B* at the extreme right. *A*, nasal breathing; *B*, mouth breathing.

THE EFFECT OF MOUTH BREATHING

If one sits erect and breathes through the open mouth the expired air is thrown directly forward; only the tip of the cone-shaped expansion lies next to the face, and a very slight motion will carry it out of the zone from which the inspired air is taken. Even the slow convection currents are usually sufficient to cause this slight motion within the necessary time limits. This results in there being practically no reinspiration with mouth breathing, unless there is such a change of position of the head as to throw the expired current downward, or unless some obstruction is brought in the way of its forward motion. The facts are well illustrated in Figure 13. This experiment was made in a room of 3,000 cubic feet with a temperature of 70 F. The ventilating air came

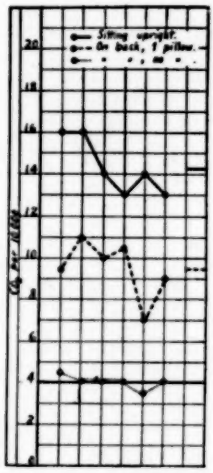

Fig. 14.—(Exp. 16). Showing the effect of position on reinspiration.

from a hallway and had constantly 5 CO_2 per 10,000. Nasal breathing is represented by the curves marked *A*, and mouth breathing by those marked *B*. The position of the body in the fourth group was that which is usually assumed when seated for writing at a table. The mouth and nasal samples were taken alternately in each of the four groups. Abundant confirmation of these results were noted in other experiments.

THE EFFECT OF POSITION

Every change of position of the head affects the line in which the expired air is directed. In the normal sitting or standing position (with nasal breathing), as has been previously stated, it is thrown downward, close to the body, and there are more or less constant upward

convection currents which tend to bring it back to the face. If the head is thrown well back the air is thrown away from the body, somewhat as it is in breathing through the open mouth, and reinspiration is lessened or prevented entirely.

The effect of such changes can be best studied by assuming the recumbent position and lowering or raising the head. Figure 14 shows three short series of observations made under these conditions in a bedroom of 1,500 cubic feet with a temperature of 64 F. While sitting on the bed, propped upright against the headboard, the reinspiration was

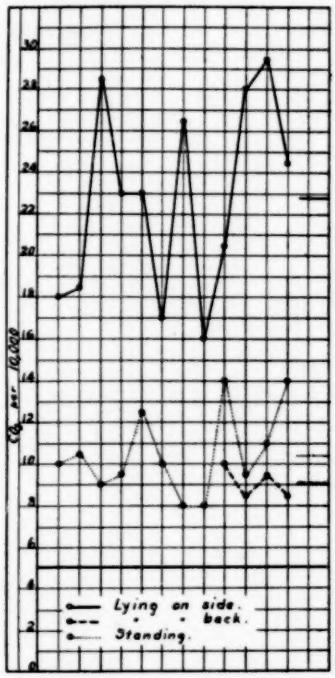

Fig. 15.—(Exp. 5). Showing the effect of position on reinspiration.

2.3 per cent.; lying down with a pillow tilting the head forward it was 1.3 per cent.; when the pillow was removed and the head thrown far back there was none at all.

It is well known that gases tend to adhere to surfaces with which they come in contact. When one lies with the side of the face on a pillow, the expired air is directed against its surface, and this adhesion will delay its removal from the immediate neighborhood of the face. Furthermore, there is the formation of pockets and dead spaces in the angles which are

not easily acted on by convection currents. The softer the pillow, and the more one's head sinks into it, the greater will be the retention. The result of lying in the position indicated is that relatively large amounts of the expired air are reinhaled. This is illustrated by the experiment shown in Figure 15, made in the same room as the preceding, with a temperature of 60 F. While standing by the edge of the bed the reinspiration was 1.2 per cent.; lying with the side of the face on the pillow it was 4 per cent.; lying on the back with a pillow under the head it was 1 per cent. In this, as in the preceding and in all other similar experiments, there

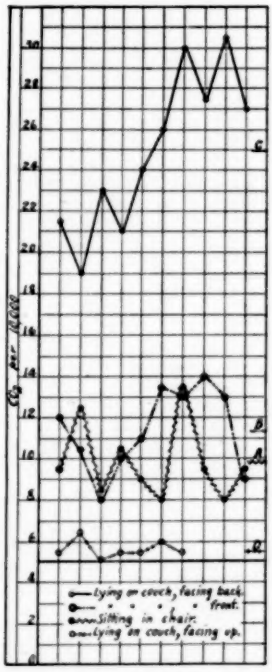

Fig. 16.—(Exp. 11). Showing the effect of position on reinspiration.

was no obstruction by blankets or other covering. The only effect of such obstructions would be considerably to increase the amount of air reinspired.

The effects of position are again illustrated by the experiment shown in Figure 16, which was carried out in a large and well-ventilated sitting room, with an open fire-place and a vigorous fire. The temperature rose while the tests were being made from 64 F. to 72 F. When sitting in a chair some 8 or 10 feet from the fire the reinspiration was 1.1 per cent.

(*A*); lying on a couch, with the face toward the edge and a little removed from it, the reinspiration was 1.4 per cent. (*B*); with the face toward the high back of the couch, and some 8 or 10 inches from it, there was 4.4 per cent. reinspiration (*C*); while lying on the back, with a very miniature pillow, there was practically none (*D*).

As might be readily inferred from the results of the foregoing experiments, it was found that ventilating currents have less effect on reinspiration in the lateral recumbent position than when the head is free. The adhesion of the expired air and the mechanical obstruction about the face

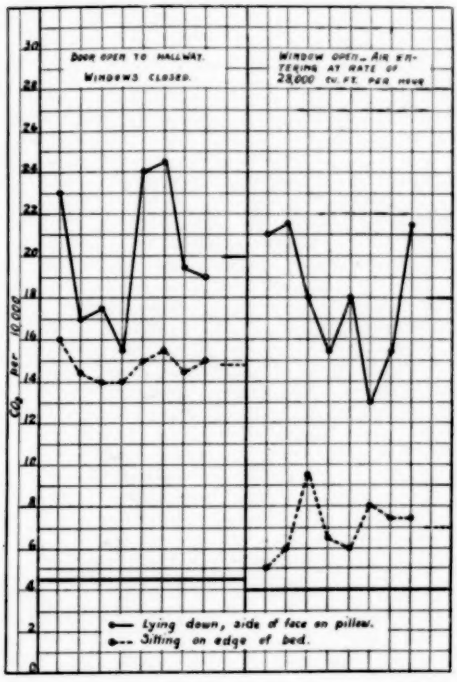

Fig. 17.—(Exp. 7). Showing effect of position and changing ventilation on reinspiration.

prevent the ready action of such currents in bringing about displacement. The condition is illustrated by the experiment shown in Figure 17. This was made in a bedroom of about 1,500 cubic feet, where the temperature was 50 F. With closed windows the reinspiration was 2.3 per cent. and 3.4 per cent. for the upright and recumbent positions, respectively; with an open window admitting air at the rate of 28,000 cubic feet per hour they were 0.7 and 3.1 per cent., respectively.

The difficulty of dislodging the expired air even by artificially produced direct currents, when one breathes over the surface of a pillow, is further illustrated in Figure 18. This experiment was made while lying on the side as in the preceding. The temperature was 70 F. The current of air was from an electric fan placed beyond the feet and nearly in line with the body, but a little behind. It was about 12 feet from the head and 2 feet above the bed. The current was measured just above the pillow — practically in the position assumed by the head when lying there. When the air was not disturbed the reinspiration was 3.6 per

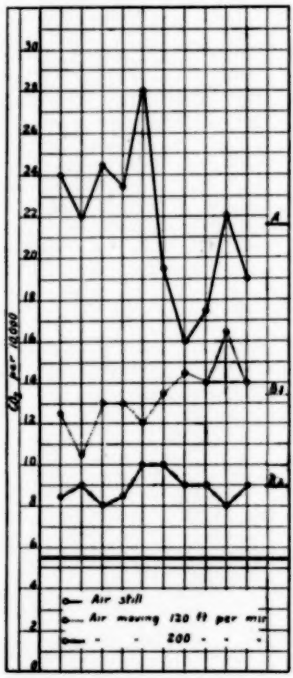

Fig. 18.—(Exp. 13). Showing the effect of air currents on reinspiration while lying with the side of the face on a pillow.

cent. (A); with a current of 120 feet per minute it was 1.8 per cent. (B_1), and with a current of 200 feet per minute it was 0.7 per cent. (B_2). With the head free and facing the breeze either of these currents is sufficient to prevent reinspiration entirely.

An air current strong enough to be felt as a breeze may still fail to remove the expired air under the above conditions, even when it flows directly at the face. This is illustrated by Figure 19. The observations

were made in the same place as the above. The temperature was 60 F. When the air was not artificially disturbed there was 2.8 per cent. reinspiration (*A*); with a fan current of 150 feet directed from behind the body there was 2.1 per cent. (*B*); and with the same current directed from in front there was still 1.1 per cent. (*C*). The breeze was quite perceptible on the face.

THE EFFECT OF INCREASING AND DECREASING CO_2

The degree of contamination in the surrounding air has practically no effect on the amount of immediate reinspiration. Any increase or decrease of the CO_2 in the general air of a room is accompanied by corresponding changes in the CO_2 of the inspired air. The gap between

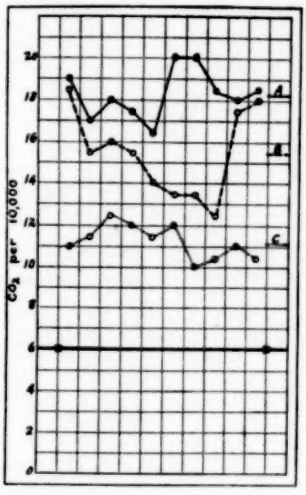

Fig. 19.—(Exp. 26). Showing the effect of air currents from different directions on reinspiration while lying on side. Air still at *A*; a current of 150 feet per minute from behind at *B*, and from in front at *C*.

the two remains about the same wherever they lie in the scale. It is understood, of course, that these statements apply only when other conditions, such as temperature and air currents, are unaltered. After Lehmann[1] had highly contaminated the air of his laboratory by burning gas, he found about the same difference in CO_2 content between this air and the inspired air that was found on other occasions when the laboratory air was relatively pure.

In order to test the matter in another way, I shut myself in an otherwise empty clothes closet of 175 cubic feet, which could be rapidly contaminated by my own expiration, and made stimultaneous observations

of the air of the room and my inspired air at five-minute intervals. After ten samples of each had been collected the door was opened and the place thoroughly fanned for ten minutes to renew the air; then six more samples of each were taken at similar intervals, the door being open, the room vacated, and the air agitated during the intervals in order to prevent any reaccumulation of CO_2, but closed while the samples were being taken. The temperature was 78 to 80 F.

During the first period of the experiment the CO_2 of the air of the room rose in a very regular curve from 6.5 to 16.5 per 10,000, and the

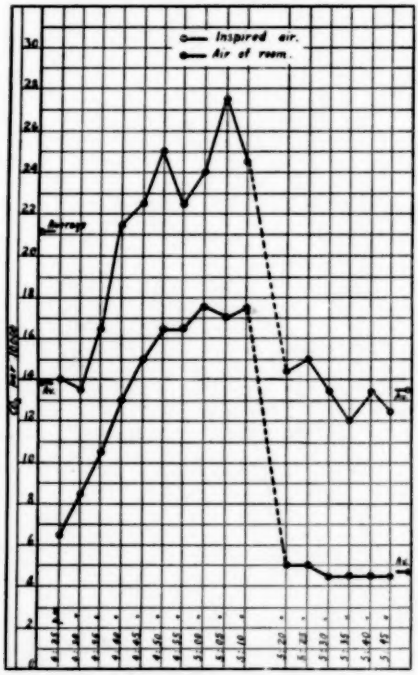

Fig. 20.—(Exp. 15). Showing that changing the CO_2 in the surrounding air has practically no effect on the amount of reinspiration.

CO_2 of the inspired air rose in an irregular but corresponding curve a like amount. During the fanning-out process the CO_2 of the air of the room fell to 5 per 10,000, near which it remained during the subsequent tests. The CO_2 of the inspired air also dropped back to about the starting point and remained there. These results are shown in Figure 20. During the first period the average reinspiration was 1.6 per cent.; during the second period it was 1.9 per cent.

The results of the first part of this experiment were verified on another occasion under similar general conditions, and in addition to the above, a sample of the air inhaled through the open mouth was taken at each five-minute period. The CO_2 of the air of the room rose from 5 to 14 per 10,000, and averaged 11 per 10,000. The CO_2 of the inspired air with nasal breathing likewise rose in an irregular curve and averaged 18.3 per 10,000, the difference (7.3 per 10,000) being equivalent to a reinspiration of 1.6 per cent. The CO_2 of the inspired air with mouth breathing followed very closely that of the air of the room; they averaged within a small fraction of each other, thus showing practically no reinspiration while breathing through the open mouth, as has been previously stated.

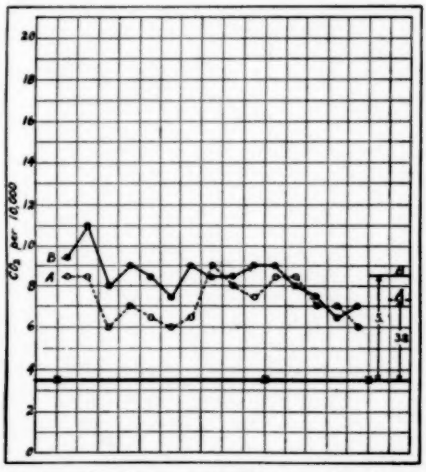

Fig. 21.—(Exp. 28). Showing reinspiration in a sleeping-porch when sitting near the center (*A*), and while lying on a bed near an open side (*B*).

THE SLEEPING-PORCH AND THE OPEN AIR

From the experiments recorded it is evident that very slight interference with the free movement of air currents about the face is sufficient to prevent the immediate removal of the expired air and to allow contamination of the air we breathe. It was believed that such interference might easily occur in the ordinary sleeping-porch, which is usually built with two open sides, or, sometimes, even in the open air. Investigation of the inspired air under these circumstances was made, and the results found to be in harmony with those previously obtained. One does not necessarily breathe pure air because he is out of doors; he is not at all likely to do so under the ordinary conditions of sleeping in tents, tent-houses, or half-open porches, such as are used for therapeutic or hygienic purposes.

An experiment carried out in a sleeping-porch 15x13x8.5 feet is shown in Figure 21. The porch has open sides to the south and east, covered by wire screens of about 12 meshes to the inch. The temperature was 70 F., and there was a breeze of 400 to 500 feet per minute in the outside air, varying in direction between south and southwest. The air of the porch, and outside of it, contained 3.5 CO_2 per 10,000, as shown by three successive determinations made in duplicate and indicated on the base line in the chart. This porch contained two beds, one of which stood near the center and opposite a door in the north wall, and one of which was close to the open east side. Two series of tests were made: one while sitting on the edge of the center bed (*A*), and one while lying on the other bed with the face about 2 feet from the screen (*B*). The reinspiration was 0.8 per cent., and 1.1 per cent. for the two series, respectively.

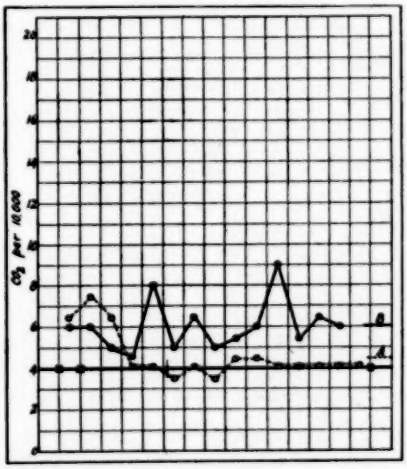

Fig. 22.—(Exp. 29). Showing the inspired air when out of doors. *A*, standing free; *B*, on an open porch.

Lehmann[1] made four observations in the outside air and found the difference between the CO_2 of the inspired air and of the surrounding air to be 0.6, 0.3, 0.8 and 0.0 per 10,000. The difference is so small as to indicate practically no reinspiration. I have made similar findings. The outside air is rarely still, and it moves in great masses. If there is no obstruction the expired air is quickly removed from the breathing zone. If one stands perfectly free there will be no reinspiration, except occasionally on very still days. But it is only necessary to step behind an obstruction of some sort to break up the progressive mass movement of the atmosphere, and the phenomenon begins again. These two conditions are shown in Figure 22. There was a light breeze blowing and the temperature was 70 F. The curve *A* shows a series of tests while

standing well away from any obstruction. Another person was standing only a few feet distant and on the windward side. It is possible that his expired air accounts for the excess of CO_2 in the first three samples of this series. The curve *B* shows a series while seated on an open porch built against the side of the house and opposite to the direction of the wind. The reinspiration is not great, but it is present. The inspired air is not pure, and the experiment serves to show how necessary it is that the air currents be free and unobstructed in order that uncontaminated air may enter the nostrils.

The experiments illustrated and referred to in the preceding represent only such conditions as are likely to be met with in daily life. With the single exception of the closet, the rooms utilized were well ventilated. Many times the air-supply was excessive. The attempt has been made to determine what kind of air is breathed under ordinary and good conditions, rather than what may be breathed under exceptionally bad conditions. It may be fairly concluded that when one lives indoors and remains quiet he will immediately rebreathe from 1 to 2 per cent. of his own expired air. When he goes to bed it will be more — from 1 or 2 per cent. to 4 or 5 per cent., depending on the position in which he lies. In some of the positions assumed by people sleeping it may even be as high as 8 or 10 per cent.; and I have once found it 18 per cent. in a single test, which did not necessitate a position by any means improbable. Nor does sleeping in the open insure pure air for breathing. The same influences here produce the same relative results that they do inside. When one buries his head between pillow and bed-clothes for the sake of warmth, reinspiration is inevitable, and it is not necessarily small in amount.

THE SIGNIFICANCE OF REINSPIRATION

The phenomenon of reinspiration has been recorded with rather less detail than was observed in the experiments, but with enough to show that it must be a very common occurrence. In order to understand its significance it is necessary to consider certain phases of the physiology of respiration.

Haldane and Priestly[4] have shown that the regulation of breathing is dependent on the concentration of carbon dioxid in the air-cells of the lungs. By the proportion of CO_2 in the air-cells the concentration of this gas in the arterial blood is determined, and the nerve cells controlling the respiratory movements are stimulated by the carbonic acid in the blood supplied to them. Hough[5] confirmed these findings. He concludes, from

4. Haldane and Priestly: The Regulation of the Lung Ventilation, Jour. Physiol., 1905, xxxii, 225.

5. Hough: Variations in the Response of Healthy Men to the Dyspneic Conditions Produced by Breathing a Confined Volume of Air, Am. Jour. Physiol., 1911, xxviii, 369.

experimental evidence, that "the increase of pulmonary ventilation is entirely the result of increase of the CO_2 tension in the blood flowing through the respiratory center"; and Henderson[6] believes that "the *capnicity* of the body [the concentration of CO_2 in the blood] is automatically maintained with a precision equalling that exhibited in the regulation of body temperature."

The carbon dioxid which is being constantly formed in the body is carried to the lungs by the venous blood. It escapes from the blood into the air-cells of the lungs, and its escape is impeded or accelerated according to the resistance it meets in them. This resistance depends on the proportion of CO_2 in the alveolar air, since the tension of this gas in the blood can fall only as low as it is on the other side of the membrane separating the blood-stream from the air-cell. The arterial blood leaves the lungs with essentially the same pressure of CO_2 that is found in the alveolar air. It is in this way that the alveolar CO_2 regulates the CO_2 tension in the blood, and so controls the respiratory movements.

Each person's breathing is so regulated as to maintain the percentage of CO_2 in the alveolar air at about 5 per cent. of an atmosphere. If the pressure falls below this, respiration is lessened or stopped until the loss is regained; if it goes above 5 per cent., the respiration is increased until the normal is restored. With light muscular work the CO_2 formed in the body will be doubled or trebled, and the breathing will be increased in like proportion so as to remove the CO_2 from the air-cells just fast enough to maintain the alveolar tension at the normal 5 per cent., but not lower. Douglas and Haldane[7] found that from lying in bed to walking five miles per hour the CO_2 output was increased twelve times, and that the alveolar ventilation was likewise increased twelve times, so that the percentage of CO_2 in the alveolar air remained practically constant. Henderson[6] found no material change in the composition of the alveolar air on going from rest to strenuous exercise; the increased production of CO_2 was perfectly compensated for by increased breathing.

Haldane and Priestly[4] found not only that the percentage of CO_2 in the alveolar air remains constant under all degrees of exertion, but that its absolute partial pressure is unaltered when the general pressure is reduced to two-thirds of an atmosphere. That the same rule holds good in the increased pressure of caissons having up to 6 atmospheres has been shown by Hill.[8] In his experiments he found the alveolar air to contain 5.4 per cent. of CO_2 at 1 atmosphere, and it gradually fell, with increasing pressure, to 0.9 per cent. at 6 atmospheres, the percentage

6. Henderson and Russell: A Simple Method for Determining the Carbon Dioxid Content of the Alveolar Air, Am. Jour. Physiol., 1912, xxix, 436.

7. Douglas and Haldane: The Dead Space of the Respiratory Passages, Jour. Physiol., 1912, Abst. in Brit. Med. Jour., Nov. 16, 1912, p. 1411.

8. Hill, Leonard: Caisson Sickness. Edward Arnold, London, 1912, p. 47.

changing in an inverse ratio to the increase of external pressure, so that the absolute tension of CO_2 in the alveolar air always remained at about 5 per cent. of the pressure of one atmosphere.

Haldane and Poulton[9] have shown that if the CO_2 is first removed from the lungs by rapid breathing, apnea may coexist with actual want of oxygen, and that breathing does not begin again until the alveolar CO_2 has returned to the normal.[10] Alveolar air normally contains about 16 per cent. of oxygen, and the red blood-cells leave the lungs practically saturated with it. The amount taken up on their next trip through the lungs depends on how much they have given up to the tissues in the meantime, not on how much is available to their use. The normal 16 per cent. of oxygen in the alveolar air is automatically maintained by the action of the CO_2 on the respiratory center, but on account of the chemical affinity of the hemoglobin for oxygen the blood-cells may still take practically their full capacity when it is reduced to 12 per cent. or less in the alveolar air. Thus a large excess of oxygen is constantly maintained in the air of the lungs. And while it is one of the chief functions of respiration to supply oxygen to the body, neither a surplus nor a deficiency of it, unless the alteration is extreme, have any effect on the respiratory movements. Breathing will not be lessened nor more oxygen taken up because more of it is supplied to the lungs; nor will the oxidation processes in the body be affected in any way, unless other influences are simultaneously brought into play.

With each breath we take back into the lungs the air contained in the nose and larger bronchi — the "dead-space" air. This dead-space air constitutes about one-third of the whole volume of quiet inspiration, and not less than one-tenth of deep breathing. To all intents and purposes it is expired air which is constantly reinspired. The phenomenon of reinspiration now under discussion is in effect simply a slight extension of the dead-space beyond its necessary limits. Rebreathing of the ordinary dead-space air is a normal and conservative process; it prevents pure air from entering the lungs and reducing the CO_2 below the amount required for stimulating the respiratory center; it makes of breathing a regular and continuous rather than an irregular and interrupted function. Douglas and Haldane[7] have recently shown that the volume of the dead-space, instead of being a fixed quantity, is automatically altered so as to give greater or less resistance to the air-flow to and from the lungs with changing exertion. They go so far as to state that rather marked variations may occur; and, while the mechanism is not fully understood, they

9. Haldane and Poulton: The Effect of Want of Oxygen on Respiration, Jour. of Physiol., 1908, xxxvii, 390.

10. Unless oxygen has fallen so low in the body that imperfect oxidation in the processes of metabolism causes the formation of abnormal acids, notably lactic, which reinforce the CO_2 in the blood for action on the respiratory center.

think the regulation is as perfect as is that of the size of the arterioles for controlling the blood-flow.

There can be no doubt that there is a large measure and a wide range of physiologic response on the part of the respiratory function to meet changing external as well as internal conditions of CO_2 concentration. It has been seen that when more CO_2 is formed in the body the respiration is automatically increased in like proportion, and in this way the alveolar CO_2 is kept at a uniform level of 5 per cent. The same thing happens when we breathe an atmosphere containing an excess of CO_2. The volume of air breathed is then increased in such a degree as, if possible, to keep the CO_2 in the alveolar air normal. Haldane and Priestly[4] found that with 2 per cent. of CO_2 in the inspired air the

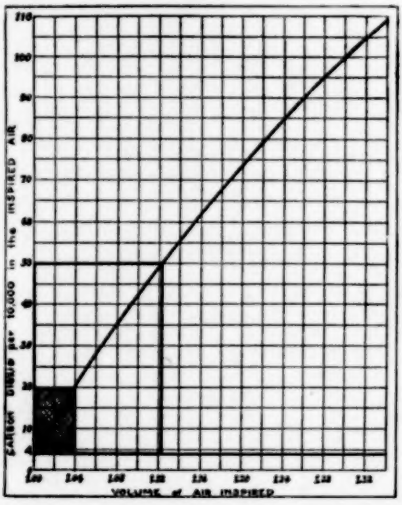

Fig. 23.—Showing the increasing depth of inspiration required to maintain a constant proportion of CO_2 in the air of the lungs, while the production of this gas in the body remains constant and its proportion in the inspired air increases.

pulmonary ventilation is increased 50 per cent.; with 3 per cent. it is increased about 100 per cent.; with 4 per cent., about 200 per cent.; with 5 per cent., about 300 per cent.; and with 6 per cent., 500 per cent. With the last the alveolar tension of CO_2 is, of course, above the normal, and this fact is signified by severe panting; but up to 3 per cent. in the inspired air the increase of breathing is scarcely noticed, unless muscular work is done, when the increased internal production of CO_2 calls for a still greater increase of the pulmonary ventilation. The adjustments are automatic and go on without our consciousness, unless an excessive increase of breathing is demanded.

If we are to maintain a constant proportion of CO_2 in the alveolar air, each inspiration must be just large enough to dilute to the same degree the CO_2 produced in the time interval of one respiration. If the amount of CO_2 produced is constant, each breath will require the same amount of air to maintain the equilibrium. But if the air used for this dilution already contains some CO_2 more will be required than if it had none; and as the amount of CO_2 in the inspired air increases, an increasingly larger amount will have to be inhaled in order to maintain the alveolar constant of dilution. Mathematical calculation shows that the volume of pulmonary ventilation required to maintain a constant proportion of CO_2 in the alveolar air, while the production of this gas by the body remains constant and its proportion in the inspired air increases, takes the form of an asymptotic curve. Figure 23 shows the form and dimensions of this curve of increasing depth of breathing for proportions of CO_2 in the inspired air ranging from 0.04 to 1.1 per cent.[11]

The normal air contains not more than 0.04 per cent. of CO_2. In well-ventlated rooms it is 0.06 or 0.08 per cent.; in poorly-ventilated rooms it may be 0.2 per cent. or more, but under very bad conditions it will rarely exceed 0.5 per cent. Including the ordinary amount of immediate reinspiration, the CO_2 of the inspired air is not liable to exceed 0.5 per cent., and it will practically never go beyond 1.0 per cent. The small shaded quadrangle at the left lower corner of the chart, therefore, includes that portion of the curve corresponding to general contamination of the air in poorly-ventilated rooms, while the heavy outline beyond this includes the portion corresponding to this contamination plus the contamination due to immediate reinspiration. Four per cent. and a fraction over 12 per cent. are seen to be the respective limits of respiratory increase required to maintain the alveolar CO_2 at a constant proportion, while 1.0 per cent. of CO_2 in the inspired air requires only 30 per cent. increase of the depth of breathing to maintain the same constant. When we remember that the possibility of increase in the depth of inspiration is 400 or 500 per cent., and that by changing the

11. The unit volume of the tidal air when the inspired air is pure (4 CO_2 per 10,000), is assumed to be one-fifth of the volume remaining in the lungs at the end of expiration. This is about the average for quiet breathing. Hough[8] and Douglas and Haldane[7] have shown that increase in the pulmonary ventilation is brought about chiefly by increasing the depth of inspiration, supplemented when necessary by an increase in the rate of breathing and then by increased expiratory effort. The curve in the chart is constructed to depth of inspiration only, and assumes not only a constant rate of production of CO_2 in the body, but a constant rate of breathing and a constant volume of air in the lungs at the end of expiration. The figures in the chart are essentially correct for the increasing minute-volume of pulmonary ventilation, whatever the change in breathing by which this is brought about, when the unit is based on the removal by the outgoing tidal air of an average production of CO_2 by the resting body, which is really the better way to express the relation.

rate and the completeness of expiration the alveolar ventilation may be increased considerably more than 1,000 per cent., it is readily understood why this slight adjustment of 4 to 12 or even to 30 per cent. falls far below the limits of our conscious effort. It has already been stated, from the experiments of Haldane and Priestly[4] that an actual increase of 100 per cent. in the pulmonary ventilation passes almost unnoticed.

In other articles I have reviewed[12] the evidence concerning volatile poisons in the expired air, a subject which has always occupied a prominent place in discussions of the air we breathe. To one who had followed the large amount of experimental investigation by many workers it seemed that the question of their existence had been finally answered in the negative in 1905, when Flügge[13] and his associates demonstrated clearly that the ill effects of confined air need no such hypothetical poison for their adequate explanation. It seemed for a time as if Weichardt,[14] by the application of some new methods of investigation, had reopened the question; but Inabe[15] and Amoss,[16] in attempting to confirm his work, have pointed out such faults of technic as practically to reverse his results and negative his conclusions. Moreover, the absence of these volatile poisons has been recently maintained by Hill,[17] who has added much new evidence and a large measure of support for the contentions of Flügge.

On the other hand, the recent experiments of Rosenau and Amoss[18] indicate that the condensed water vapour of the human breath may contain a trace of organic matter belonging to the protein group. When this fluid was injected into animals about one-fourth of them were so sensitized that a subsequent injection of human blood-serum gave a distinct anaphylactic reaction. This work will undoubtedly be repeated and confirmed, or another explanation offered. No volatile proteins have been previously known, none have been otherwise demonstrated in the breath, and the condensed water itself has no toxic effect when injected into animals. And when we remember that so small a quantity of egg albumin as 1-20,000,000th of a milligram[19] is sufficient to confer a similar

12. Crowder. THE ARCHIVES INT. MED., 1911, vii, 85; Trans. of the Section on Preventive Medicine and Public Health, Am. Med. Assn., 1911, 177; THE ARCHIVES INT. MED., 1913, xi, 66.

13. Flügge, Heymann, Paul, Erelenz: Ztschr. f. Hyg., 1905, xlix, 363, 388, 405, 433.

14. Weichardt: Arch. f. Hyg., 1908, lxv, 252; 1911, lxxiv, 185.

15. Inabe: Ueber das Kenotoxin Weichardts in dem Ausathmungsluft, Ztschr. f. Hyg., 1911, lxviii, i.

16. Amoss: Organic Matter in the Expired Breath, Jour. of Exper. Med., 1913, xvii, 132.

17. Hill, Leonard: The Influence of Ozone in Ventilation. Jour. Royal Soc. Arts, 1912, lx, 344.

18. Rosenau and Amoss: Organic Matter in the Expired Breath, Jour. Med. Research, 1911, xxv, 35.

19. Wells: Studies of the Chemistry of Anaphylaxis, Jour. Infect. Dis., 1908, v, 449.

sensitization, it would seem that there may be possible sources of error quite difficult to control entirely.

But leaving all this aside, suppose for the moment that the breath does contain a protein — or any other waste organic substance — it still does not appear that a little reinspiration could be harmful. In the alveolar air this substance would necessarily be present in relatively high concentration, but always a lower concentration than the blood or tissues from which it comes. At the end of expiration it would fill the dead-space in like concentration, as must any gas excreted into the lungs, and the dead-space air is all drawn back with each breath as a part of normal breathing. We cannot directly increase the concentration of this hypothetical substance in the blood by breathing an atmosphere containing a lower concentration of it; we can only hinder its escape. But in this there is a necessary relation between any such hypothetical body in the expired air and the CO_2, as well as a striking analogy to CO_2 as a poison which has been clearly drawn by Sewall.[20] We cannot rebreathe expired air without rebreathing CO_2, and rebreathing CO_2 causes deeper inspiration. The alveolar concentration of any gaseous constituent of the expired air must therefore be subject to the same laws of compensatory change in the pulmonary ventilation as are determined by the CO_2. Our hypothetical substance would be regulated to whatever may be at any time its normal proportion simultaneously with, and by the action of, the CO_2. And the quantitative values of the curve presented in Figure 23 will apply exactly to any other volatile excretion into the air-cells by substituting for CO_2 the percentage of expired air represented by the CO_2. Let us assume that it were possible, by higher concentrations of our hypothetical organic body, to poison the animals producing it; it is possible also to poison them by CO_2 — or even by oxygen — but far from being harmful in its normal concentration CO_2 is a prime necessity; and the remarkable adaptibility of the respiratory function enables the body to maintain a normal concentration under a great variety of conditions. Regulation is automatic, and, according to our present physiologic conceptions, necessarily takes place. The adjustment demanded by the ordinary amount of reinspiration is relatively very small, and it would seem that it must lie well within the margin of safety which Melzer[21] has so well described as belonging to all well-understood physiologic processes.

It is commonly, though erroneously, supposed that the good effects of efficient ventilation are due to the chemical purity of the air. When attention was called to the occurrence of immediate reinspiration it was looked on as a newly discovered source of impurity in the air we breathe.

20. Sewall: On What Do the Hygienic and Therapeutic Virtues of the Open Air Depend, Jour. Am. Med. Assn., 1912, lviii, 174.

21. Melzer: Factors of Safety in Animal Structure and Animal Economy, Harvey Lectures, New York, 1907-8, p. 139.

To this previously unrecognized source of contamination was attributed much of the failure that has so often attended attempts to bring comfort out of ventilating procedures, and from this has arisen the "theory of displacement" in its application to ventilation. Accepting the old notion that chemical purity is a proper basis for ventilation standards, and assuming that reinspiration is necessarily harmful, some of the hygienists propose to handle the air supplied to a room in such a manner that the expired air will be immediately carried away from the face and cannot be rebreathed. It is asserted that if the new principle is applied a much smaller quantity of air than is demanded by the older quantitatve or dilution standards can be made to yield hygienic results. But small quantities of air do not lend themselves readily to maintaining the currents that have been shown to be necessary in order to accomplish the displacement aimed at. Or, if the necessary currents are maintained, and throughout a sufficient area to be effective, it becomes a physical necessity to recirculate the air; thus only delaying rather than preventing reinspiration, and reducing the system to one of simple dilution, which it is the avowed purpose to avoid. By actual experiment I know that the plan most widely heralded does just this thing so far as the contamination of the air of a room is concerned, and it is improbable that immediate reinspiration is materially restricted. The theory of displacement does not sufficiently take into consideration that all animals possessing lungs ventilate them on a very simple principle of dilution; nor does the pure air theory sufficiently consider that the air of the lungs always remains highly contaminated with their own excretory gases, and that there is such an effective barrier as the dead-space against the lowering of the contamination.

If it is desired to prevent reinspiration, ways have been indicated by which this may be done. The results will be good, bad, or indifferent, according to the plan chosen; but in no case will the results, whether good or bad, depend on the fact that reinspiration is prevented. Within a wide range of variation in the purity of the air we breathe (in so far as the purity is effected by the products of respiration), the respiratory function is perfectly adapted to maintain its normal balance. The only apparent effect of rebreathing a little of our own expired air is a slightly deeper inspiration.

But ventilation is not a matter of little consequence because of this. It is still just as important as it has always been considered; the benefits of fresh air and the outdoor life are beyond question. But these measures should be carried out in the interest of the heat economy of the body rather than with regard to the chemical purity of the air we breathe. The good effects of the outdoor air depend on its coolness, its motion and its relative humidity. These physical qualities enable it to absorb the

heat which is constantly being formed in the body, and which must be as constantly removed. Air that will take it up rapidly will stimulate healthy functions; air that takes it too slowly leads to sluggish metabolism, and if maintained will ultimately result in a low resistance to disease.

The rigor of a temperate or a colder climate makes of its inhabitants a house-dwelling race. They very commonly over-heat their houses, if not by fire and steam then by the heat of their own bodies; and when they do this they complain of poor ventilation, regardless of whether the air-supply is large or small. Whichever this may be, under any conditions that are likely to arise, there will still be oxygen in excess of every demand, and the CO_2 will still find a ready escape from the blood; but in an over-warm atmosphere the body heat will be stagnated and the consumption of oxygen by the tissue cells will be decreased. Ventilation is necessary in order to maintain the thermic balance of the body and to stimulate its chemical activity; and ventilation with cool air is especially desirable. A little extension of the dead-space beyond the tip of the nose is of no consequence. In spite of this extra contamination of the inspired air, the proportion of CO_2 in the alveolar air will remain a little lower in a warm room than in the invigorating cold of the out-of-doors, as has been shown by Boycott and Haldane.[22] It will remain so because metabolism is reflexly retarded by a warm aerial envelope, the consumption of oxygen by the tissues and the production of CO_2 by them being much less in warm air than in cold.

That this discussion concerning the significance of reinspiration applies only to healthy persons scarcely needs to be added. The capacity of the lungs may become so restricted by disease that the slightest addition to their work is undesirable. But when we learn that they are still capable of performing the respiratory function with the capacity reduced to so little as one-sixth of the normal,[23] the margin of safety is seen to be a very generous one.

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22. Boycott and Haldane: The Effects of Low Atmospheric Pressure on Respiration, Jour. Physiol., 1908, xxxvii, 355.

23. Bernard et Mantoux: Capacité pulmonare minima compatible avec la vie, Jour. de physiol. exper., 1913, xv, 16; (Ed. Abstr. in Jour. Am. Med. Assn., 1913, lx, 1794).

FUNCTIONAL TESTS OF THE KIDNEY IN UREMIA*

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In any disease in which the diagnosis cannot be reduced to something like certainty, the prognosis must evidently be considered with some reservation. If in addition diagnosis and prognosis are alike made dependent on laboratory tests, either these procedures must be of demonstrated accuracy and especial relevance or else we shall be led into blunders in diagnosis or faulty deductions in our conceptions of the nature of the disorder.

In relation to uremia, I wish to call attention to certain limitations of laboratory aids, and to exceptions which many cases present to what is perhaps a doubtful average, since by constancy of iteration some of these tests bid fair to be accepted as criteria.

Now, in the conditions we call uremia the clinical manifestations cover a wide range, and in proportion as the picture is varied and changeable the difficulties of correct interpretation are increased. It is just because there is no definite symptom-complex, no fixed association of physical signs correlated with uremia, that its recognition is often held to be simple, and yet the necropsy fails to confirm the diagnosis. In the absence of a more clearly defined clinical entity during life we must depend ultimately for the criterion on the anatomical changes found by the pathologist after death. The only exception, possibly, should be in those cases that have been under observation for long periods before the advent of uremia and in which this state is the logical culmination of events.

The cause of uremia is not known, but the common conception relates the condition to nephritis; whether by functional failure of the kidneys or otherwise, does not at present matter. At necropsy marked renal degeneration is requisite for confirmation of the diagnosis, and with this usually is found edema of the brain and often colitis. Since it is the conception of uremia that it is intimately related to severe nephritis and represents the *denouement* of a pathological process dependent on renal disease, or of which renal disease is an invariable accompaniment, it follows that the value of a test having for its aim the estimation of renal function, can be measured by the results elicited in demonstrated cases

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of uremia. If this assertion be not correct the only alternative is that uremia is not necessarily related to renal function.

The functional test for the kidneys that is being most generally employed by both internists and surgeons in America is that of phenolsulphonephthalein. In many cases of uremia the results secured by this test accord with the clinical data secured by other procedures. Cases of uremia often fail to eliminate in two hours enough of the substance to permit of quantitative estimation, and such patients sometimes die, sometimes improve sufficiently to leave the hospital. But there are notable exceptions in the operation of the test to which I wish to call special attention.

I shall cite but three cases representing three different types of nephritis.

CASE 1.—E. P., aged 53, was refused life insurance in 1909 in consequence of which he came to his physician; examination revealed moderate secondary anemia, cardiac hypertrophy without valvular disease, blood-pressure 190, arteriosclerosis and enlarged liver. The urine was increased in amount; nycturia was present. In a twenty-four-hour specimen, 2,300 c.c., there was albumen, 1+ grams per liter, many granular casts and leukocytes. Diagnosis, secondary contracted kidney. In November, 1911, marked albuminuric retinitis developed. During December diarrhea was an obstinate symptom. The phenolsulphonephthalein test resulted in 53 per cent. being recovered in two hours. During January marked improvement took place. Another phenolsulphonephthalein test showed 55 per cent. recovery. There was apparently gradual improvement till the middle of February, when after one day of headache the patient had a severe convulsion; coma supervened and continued till death, thirty hours later. Postmortem: Anatomical diagnosis, chronic nephritis (red granular kidney), cardiac hypertrophy and dilatation, pulmonary edema, cerebral edema.

CASE 2.—C. H., aged 46, was admitted to hospital four days before death complaining of extreme vertigo and cramps in the legs. On admission the patient was drowsy and in twenty-four hours there was coma. Examination was negative except for retinal hemorrhages; heart not hypertrophied; blood-pressure 130; respiration normal in character and rate; incontinence of urine; catheterized specimen contained a trace of albumin and an enormous number of casts. Phenolsulphonephthalein test gave 63 per cent. recovery in two hours. Clinical Diagnosis: Chronic interstitial nephritis, uremia. Anatomical Diagnosis: Chronic nephritis, small granular kidney, cardiac dilatation, ulcerative colitis, edema of brain.

CASE 3.—B. F., aged 33. For a month there had been increasing dyspnea and swelling of abdomen and ankles. Examination showed moderate general anasarca, some fluid in abdomen and both pleural cavities. Heart normal, blood-pressure average, 98 millimeters of mercury. Retinae normal. Urine: Average twenty-four voidings 1,100 c.c. Albumin constantly over 2 per cent.; many granular casts; some red blood-cells; chlorids diminished. Clinical Diagnosis: Parenchymatous nephritis.

The course of the disease appeared favorable, as the edema subsided rapidly, several phenolsulphonephthalein tests were done along with other tests; the last, eleven days before death, showed a recovery of 57 per cent. in two hours. Without prodromal symptoms other than slight nausea this patient had a severe convulsive seizure lasting nearly an hour and died shortly after. Anatomical Diagnosis: Chronic parenchymatous nephritis; large white kidney; cerebral edema; edema of lungs.

These cases represent the types of renal lesion that we most often meet. The diagnosis was made correctly in each instance and was proved by necropsy. The phenolsulphonephthalein test gave a figure approximating normal in all, yet, in view of the termination of each case, one would hardly venture to assert that the renal function was normal. As to prognosis, this test would have indicated that recovery was almost certain. Granting that in many cases, perhaps the majority, the results of this test harmonize with the clinical picture and the course of events, we must assuredly find out in what percentage of cases of renal disease we are apt to be misled before we can venture any opinion whatever as to the clinical value of the test either diagnostically or prognostically. Does not the record of the above-cited cases suggest that the excretion of phenolsulphonephthalein depends on some other factor (circulation?) than pure renal disease, which by its presence or absence determines the rate of secretion by the kidney? Non-protein nitrogen of the blood?

In the last few years there is notable in the literature, especially that of Germany, an ever-increasing insistence on the significance of the non-protein nitrogen (residual, filtrate, incoagulable nitrogen) of the blood. It is to be recalled that this is no new method of studying nephritis, although our technic at present may be better than formerly. Bright's cases were investigated by Babbington. Von Jacksch, Hoppe-Seiler, and Ascoli made many determinations on all sorts of cases and came to various opinions. Here too we have to do with a factor of degree. When the non-protein nitrogen is so large, as in some cases up to 200 milligrams per 100 cubic centimeters of blood, the outcome for the patient is pretty definitely bad. But those figures even in uremia are not the rule, and it must also be definitely stated that it is not at all unusual to find the non-protein nitrogen within the normal variation in cases of chronic interstitial nephritis with high blood-pressure — the very type of case in which the method is supposed to be of greatest clinical significance.

The normal limits for the non-protein nitrogen of the blood are according to various authors between 20 and 40 milligrams per 100 cubic centimeters. For normal controls I have utilized cases in the surgical service such as fractures and hernias, in which there was no evidence of renal or cardiovascular disease. With these individuals the average non-protein nitrogen is 32 to 33 milligrams in 100 cubic centimeters of blood, with 44 milligrams as a maximum.[1] Strauss believes that in parenchymatous nephritis the non-protein nitrogen is usually low, which is probably correct in cases of purely tubular involvement in which the process has not been of long duration, but the non-protein nitrogen is

1. The average non-protein nitrogen in seventy-two cases of uremia in my series was 87 mg. per cent.

occasionally low in cases of contracted kidney also. Figures under 40 milligrams in 100 cubic centimeters of blood in these cases with uremia are not very exceptional in my series.

One is then confronted not by a positive fact which excludes uremia, but by a negative observation to be interpreted along with other clinical data. No one has gone to such arbitrary extremes as Widal,[2] who, in a recent publication classifies uremia according to retention theories: (1) Those patients who retain NaCl and develop edema (*chlorurémique*). (2) Those who show nitrogen retention; that is to say, have an increase in the non-protein nitrogen of the blood (*azotémique*). (3) A combination of the two above classes.

As to the type azotémique, it is set forth that when the non-protein nitrogen is 50 to 100 milligrams in 100 cubic centimeters of blood, the prognosis is not immediately fatal; above 100 milligrams, it is to be estimated in months and weeks. Then what is to be said of the following?

CASE 4.—A. T., aged 54. Slowly failing health for several months; notable in loss of strength; rapid fatigue on exertion and slight dyspnea; no history of edema. Three days before admission to hospital, severe vertigo. For two days there was some headache and the patient felt very drowsy.

Examination showed retinal hemorrhages, very slight cardiac hypertrophy, blood-pressure 140 to 150 millimeters of mercury, urine 500 to 800 cubic centimeters for twenty-four hours with a trace of albumin and many casts. No edema or fluid in cavities. Non-protein nitrogen, 28 milligrams in 100 cubic centimeters of blood.

The drowsiness deepened into stupor and after two days, coma. Death occurred on the fifth day after admission. Clinical diagnosis, uremia. Anatomical diagnosis, chronic nephritis (extremely small granular kidneys), edema of brain, marked colitis, uremia.

In this case it is evident that had undue weight been given to the low non-protein nitrogen one would have been led to conclude that there was not a severe nephritis, and that the retinal condition was due to some intracranial disease. Moreover, after the diagnosis of uremia had been made the non-protein nitrogen would have pointed, according to Widal, to a favorable outcome.

Tests and methods of investigation such as those I have discussed are undoubtedly valuable. Correctly applied they stimulate interest and lead in the long run to broadened knowledge. But just so soon as such methods are regarded as ultimate criteria, we are led first into errors in diagnosis, and from that creep into narrowed medicine and false ideas as to the pathology of a disease entity.

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2. Widal, Fernand: Le Mouvement Medical, 1913, i, 1.

BLOOD-PRESSURE STUDIES IN TUBERCULOSIS AT A HIGH ALTITUDE. REPORT OF SIX HUNDRED CASES*

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Six years ago one of us (Peters) began the study of blood-pressure in tuberculous individuals living under sanatorium conditions at an elevation of 6,000 feet. A preliminary report[1] was made in 1908 covering a series of one hundred cases. The findings at that time were in such marked contrast to the work of other observers, notably Gardiner and Hoagland[2] of Colorado Springs, that we decided to continue our observations until we had obtained readings in a sufficient number of cases to make the conclusions of some value from a scientific standpoint.

With this idea in view we have made records covering a series of six hundred cases, and are gratified to note that the conclusions reached in our earlier report are even more strongly borne out by a more exhaustive research.

The question of blood-pressure in tuberculosis has usually been dismissed with the dogmatic statement that the disease tends toward hypotension. The observations of workers at sea level have confirmed this statement many times over, but on the other hand, little work has been done along the same line at elevations considered especially adapted for the treatment of consumption. True, the work of Gardiner and Hoagland[2] already cited tends to show that altitude lowers blood-pressure, but the number of cases reported is far too small to allow of radical conclusions. Also, a number of the experiments were made on the top of Pike's Peak, at an elevation of over 14,000 feet, and from the difference in elevation alone would be of little value in a comparison with our results. We are willing to grant that on coming to a high altitude the pressure drops temporarily, but on residence a gradual rise is noted. This very fact, the sudden change from a moderate elevation to an altitude of over 14,000 feet, may probably account for the difference in our conclusions and those of Gardiner and Hoagland.

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* From the laboratory of the New Mexico Cottage Sanatorium.

1. Peters, L. S.: THE ARCHIVES INT. MED., 1908, ii, 42.
2. Gardiner and Hoagland: Trans. Am. Climatol. Assn., 1905.

Now let us consider the work of Crile.[3] By means of a pneumatic cabinet he was able to show a rise in pressure when the surrounding atmospheric pressure was decreased. Along the same line may be mentioned the work of Lazarus and Schirmunski,[4] Bert[5] and many other observers. F. H. Bartlett[6] has investigated the effects of breathing rarified air in rabbits and finds that the aortic pressure falls with that of the inspired air after a sufficient negative pressure has been produced. Bert,[5] however, says that the technical difficulties render exact experiments in this respect impossible. Coagulation in the connecting piece between artery and manometer will always take place.

Mosso[7] made his studies on the top of Mount Rosa at an altitude of 4,560 meters. He found very little difference in readings at this elevation and sea level. Here again we make the same criticism of too high altitude. However, Mosso cites the work of K. Heller, W. Mayer and H. von Schroetter,[8] who, at an altitude of 2,210 meters, found a rise in pressure. This latter elevation more nearly coincides with the altitude at which our results were obtained. Further references could be given, such as the work of Frankel and Geppert,[9] who found that the pressure did not change with very considerable fall in atmospheric pressure even when of a nature dangerous to life. In one experiment in which the barometer showed 214 millimeters there was an increased blood-pressure and slowing of the pulse.

Liebig[10] states that results of observations on the effect of barometric pressure on blood-pressure are not uniform. He found that with a fall in atmospheric pressure the blood-pressure rose in three people, in one at a pressure corresponding to 2,800 meters altitude; in another under atmospheric pressure at 520 mm., and in a third in a pressure corresponding to 3,400 meters altitude. In a more extensive fall of atmospheric pressure, or otherwise a much higher altitude, the blood-pressure fell. This latter seems to coincide with the observations of Gardiner and Hoagland[2] in our country, namely, that in too high an elevation we get a reduction in blood-pressure.

The criticism we wish to make on all observations to which we have thus far referred is briefly stated thus: 1. The number of experiments and the number of people experimented on are far too small to warrant of any radical conclusions. 2. No comparison can be made between

3. Crile, Geo. W.: Blood-Pressure in Surgery, Phila., 1903, p. 283.
4. Lazarus and Schirmunski: Ztschr. f. Klin. Med., 1884, vii.
5. Bert: La Pression Barometrique, Paris, 1878.
6. Bartlett, F. H.: Am. Jour. Physiol., 1903, x, 143.
7. Mosso, A.: Arch. ital. di biol., 1905, xliii, 341.
8. Heller, K., Mayer, W., and von Schroetter, H.: Ztschr. f. klin. Med., xxxiii.
9. Frankel and Geppert: Ueber die Wirkungen der verdunnten Luft. auf den Organismus, Berlin, 1883, p. 65.
10. Liebig: Sitzungb. d. Gesellsch. d. Morphol. u. Biol., 1896, xii.

observations on animals under pneumatic cabinet conditions and the observations on tuberculous invalids at 6,000 feet elevation. 3. No comparison can be made between observations made on man at extremely high elevations and on those made on tuberculous invalids at 6,000 feet elevation. 4. Pneumatic cabinet experiments on man cannot in any way prove or disprove the results of observations on tuberculous invalids residents of an elevation of 6,000 feet.

Referring now to the more recent work in this country of Haven Emerson.[11] He conducted a series of experiments on both man and animals to determine the causes of hypotension in tuberculous patients, and to determine the value of such symptoms as a diagnostic and prognostic measure. He concludes that the cause of hypotension is primarily a toxic action on the vasomotor center in the medulla, allowing of a vaso-paresis, or stimulating a vaso-dilatation, and secondarily, progressive cardiac atrophy or degeneration. He believes that hypotension is common enough in early cases to be sought for as carefully as is the custom at present to search for pulmonary signs. He draws about the same conclusion regarding prognosis as was contained in our earlier report,[1] namely, with betterment of pulmonary condition the blood-pressure is increased; stationary patients show little or no change, and progressive patients show a decrease in blood-pressure findings.

Ritter[12] also bases much on the prognosis from the blood-pressure observations and his work is based on records made on ambulatory patients treated at the out-patient department of Rush Medical College.

These last two observers — Emerson and Ritter — were working at sea level and with no intention of making a comparative study of observations there and at high altitudes. With their work we must also refer to that of Thayer[13] of Baltimore, and we shall use the latter two reports in making our comparison of average pressure since Emerson gives no adequate figures.

Considering all classes of cases our results show that at an elevation of 6,000 feet the average pressure in consumptives is 132 mm. of mercury. Thayer's averages for the same class of patients at sea level is 103 mm. of mercury, and Ritter's is 110 mm. From observations made here on normal individuals we find the average pressure to be 143, all ages considered from 19 to 66. Even this is a higher average than the majority of observers give for normal individuals at sea level.

On first coming to a high elevation the pressure is lowered, but after a short residence an increase is noted and in a majority of patients an increase over the original reading at sea level.

11. Emerson, Haven: THE ARCHIVES INT. MED., 1911, vii, 441.
12. Ritter, John: Trans. Nat. Assn. for the Study and Prevention of Tuberculosis, 1911, p. 297.
13. Thayer, Wm.: Cited by Stanton, Internat. Clinics, 1907, iii, Series 17.

From a prognostic standpoint we believe the blood-pressure findings are of great value in tuberculosis. Here, we have noted that if the patient continues to improve his pressure gradually rises. If no improvement is noted, but on the other hand, the status is stationary, the pressure remains practically the same. If the patient's condition grows worse there is a decrease in the blood-pressure reading.

We find also that the degree of involvement bears no relation to the pressure, and for that reason we have omitted a reference in the general table to the Turban classification and have classified our cases from the standpoint of toxemia. We note that a marked relation exists between blood-pressure and the degree of toxemia. Here also the inverse ratio of pulse and pressure noted by so many observers is clearly shown — a high pulse accompanied by a low pressure, and a low pulse by a normal or higher pressure.

We have also studied, in a limited number of cases, the relation of blood-pressure and pulmonary hemorrhage. Although we have been unable to observe readings immediately before the hemorrhage occurred, we know from records taken immediately after, that the pressure is increased from 15 to 25 mm. of mercury. It is only reasonable to suppose that such increase occurred before the hemorrhage and was the immediate cause of the bleeding. These cases are so few in our experience that we have not incorporated them as such in our table, but merely state the facts as we have seen them, hoping to gain some information in the future and be able to substantiate our observations by a sufficient number of cases to warrant our conclusions. Just why we have so few hemorrhages at this elevation with our increased pressure is an open question. The two facts seem to be in direct contradiction. However, the lowered blood-pressure on arrival, together with a relaxed circulatory system, gives the body time to accommodate itself to the change, and owing to the stimulating effect of altitude on cardiac and vascular tone the walls of the capillaries and circulatory system in general are strengthened and are better able to stand the increased pressure which afterwards results. It is a well-known fact that patients bleeding at sea level over a long period of time (having been placed on a train during this series), on arrival in the elevation of the southwest have been surprised to find such hemorrhages cease and never occur again.

Heretofore the knowledge of climate in the treatment of tuberculosis was empirical. Consumptives were sent west and made a recovery, or were buried on the plains and hillsides in a strange country. The laity and physicians have granted from time immemorial the value of climate in the treatment of tuberculosis. Some early observer before the time of Hippocrates, wisely said: "If you would get well of consumption go into the mountains and live on the fruit of the cow," and opinion has

TABLE 1.—Data Concerning Six Hundred Consumptives

Case No.	Age	Sex	Blood Pressure		Pulse Av.	Temp. F. Av.	Urine	Degree of Toxemia	Status on Discharge
			Ad.	Av.					
1	32	M	106	126	80	98.6	N	—	Arrested
2	18	F	101	109	90	98.6	N	—	Improved
3	25	M	102	118	80	98.6	N	—	Improved
4	27	M	112	124	76	98.6	Alb. Casts	—	Improved
5	27	M	100	91	80	100.0	N	++	Progressive
6	27	M	104	98	140	102.0	Alb. Casts	+++	Progressive
7	43	F	130	130	?	99.0	N	+	?
8	22	F	108	116	85	98.0	N	—	App. Cured
9	28	M	125	142	80	99.0	Casts	+	Arrested
10	34	M	113	116	84	98.6	N	—	Arrested
11	25	M	128	102	80	98.6	N	—	Unimproved
12	18	M	121	121	80	98.6	N	—	Unimproved
13	33	M	100	106	104	99.6	Alb. Casts	+	Progressive
14	54	M	132	126	100	98.6	N	—	Unimproved
15	29	M	112	100	100	101.0	N	+++	Progressive
16	47	M	126	148	84	98.6	N	—	Arrested
17	24	F	103	119	70	98.6	N	—	App. Cured
18	29	M	120	130	90	99.0	N	+	Improved
19	32	M	94	90	84	98.6	N	—	Arrested
20	23	F	104	104	80	98.6	N	—	Improved
21	23	M	104	134	75	98.6	N	—	Arrested
22	35	M	112	112	102	98.6	Alb.	—	Improved
23	22	M	110	120	98	98.6	N	—	Arrested
24	37	M	112	124	80	98.6	N	—	Arrested
25	24	M	117	117	128	98.6	N	—	Unimproved
26	25	M	130	132	74	98.6	N	—	App. Cured
27	28	F	119	120	80	98.6	N	—	Improved
28	44	M	135	144	104	98.6	N	—	Arrested
29	37	M	102	110	90	98.6	N	—	Improved
30	42	M	118	110	100	98.6	N	—	Improved
31	30	M	120	150	100	98.6	N	—	Improved
32	28	M	134	176	80	99.4	Alb. Casts	+	Unimproved*
33	28	M	110	126	120	98.6	N	—	Arrested
34	40	M	134	144	90	99.0	Alb	+	Arrested
35	48	M	114	120	75	98.6	Casts	—	Arrested
36	29	M	86	120	76	98.6	N	—	App. Cured
37	25	M	122	138	88	98.6	N	—	App. Cured
38	19	F	122	126	90	98.6	N	—	Improved
39	27	M	122	130	80	99.0	Casts	+	Improved
40	22	M	134	144	90	98.6	Casts	—	Arrested
41	29	M	138	140	90	98.6	Casts	—	Arrested
42	25	M	90	124	100	99.8	N	+	Improved
43	23	M	120	110	90	98.6	Casts	—	Progressive
44	28	M	110	110	85	98.6	N	—	Unimproved
45	21	M	106	118	132	99.2	Aib. Casts	+	Improved
46	40	M	130	172	95	99.0	Casts	+	Arrested
47	25	M	134	130	90	98.6	N	—	Arrested
48	40	M	160	158	95	100.0	Casts	++	Unimproved
49	34	M	96	110	80	98.6	Casts	—	App. Cured
50	23	M	112	118	90	98.6	Casts	—	Improved
51	52	F	122	140	84	98.6	N	—	App. Cured
52	24	M	130	142	90	98.6	Casts	—	Improved
53	58	M	110	126	92	98.6	N	—	App. Cured

* Kidneys responsible for high blood-pressure.

TABLE 1.—Data Concerning Six Hundred Consumptives—(Continued)

Case No.	Age	Sex	Blood Pressure		Pulse Av.	Temp. F. Av.	Urine	Degree of Toxemia	Status on Discharge
			Ad.	Av.					
54	29	F	130	130	84	98.6	Casts	—	Improved
55	28	M	110	100	112	99.4	Casts	+	Progressive
56	23	M	130	128	70	99.0	Casts	+	Improved
57	52	M	164	150	138	99.0	Alb. Casts	+	Unimproved
58	49	M	136	144	100	98.6	Alb. Casts	—	Arrested
59	29	M	120	120	120	100.0	N	++	Improved
60	28	M	110	130	108	98.6	Casts	—	App. Cured
61	35	F	128	130	108	98.6	N	—	Improved
62	33	F	110	102	110	98.6	N	—	Progressive
63	22	F	110	124	92	98.6	N	—	Improved
64	31	M	98	140	100	98.6	N	—	Improved
65	48	M	134	140	84	99.1	Alb. Casts	+	Arrested
66	24	M	128	134	85	98.6	Casts	—	Improved
67	42	F	110	126	120	99.0	Alb. Casts	+	Improved
68	40	M	130	148	80	98.6	Casts	—	Arrested
69	36	F	150	150	100	98.6	N	—	App. Cured
70	27	F	106	120	88	98.6	Casts	—	App. Cured
71	38	M	88	110	80	99.4	Casts	+	Improved
72	27	M	119	128	75	98.6	N	—	Arrested
73	32	M	110	128	75	98.6	N	—	Arrested
74	24	M	100	126	80	98.6	Casts	—	Arrested
75	30	F	110	140	80	98.6	N	—	App. Cured
76	40	M	106	118	100	99.2	N	+	Improved
77	46	M	134	150	80	98.6	N	—	Improved
78	35	M	148	160	85	99.0	Alb. Casts	+	Unimproved
79	35	M	118	140	75	99.5	N	+	Improved
80	35	M	122	122	110	98.6	N	—	Unimproved
81	29	M	130	134	80	98.6	N	—	Improved
82	45	M	142	148	120	99.0	N	+	Arrested
83	42	M	146	154	80	98.6	Casts	—	Improved
84	26	M	96	130	80	98.6	N	—	Improved
85	25	M	110	120	80	98.6	N	—	App. Cured
86	22	M	88	112	75	98.6	N	—	Arrested
87	28	F	112	112	100	98.6	Casts	—	Progressive
88	39	M	113	120	100	98.6	N	—	Arrested
89	28	M	102	126	85	98.6	N	—	Arrested
90	40	F	108	108	90	100.0	Alb. Casts	++	Progressive
91	37	M	114	134	85	98.6	N	—	Arrested
92	25	M	108	124	85	98.6	N	—	Arrested
93	23	M	128	128	75	98.6	Casts	—	App. Cured
94	26	M	130	135	85	98.6	N	—	Arrested
95	36	F	102	122	90	98.6	N	—	Arrested
96	34	M	106	116	120	99.4	N	+	Improved
97	47	M	108	120	100	99.4	Alb. Casts	+	Improved
98	18	F	128	136	100	98.6	N	—	Improved
99	27	F	130	138	88	98.6	N	—	Arrested
100	28	M	114	146	80	98.6	Alb. Casts	—	Improved
101	26	M	125	125	90	101.0	N	+++	.....†
102	23	M	125	145	90	99.0	N	+	Arrested
103	33	M	100	116	90	99.6	N	+	Improved
104	41	M	140	150	85	99.2	Hyn. Casts	+	App. Cured
105	28	M	130	130	85	98.6	Casts	—	Progressive
106	23	M	125	130	90	98.6	Casts	—	App. Cured
107	29	F	118	130	80	99.2	N	+	App. Cured

† Died following hemorrhage.

TABLE 1.—DATA CONCERNING SIX HUNDRED CONSUMPTIVES—(Continued)

Case No.	Age	Sex	Blood Pressure		Pulse Av.	Temp. F. Av.	Urine	Degree of Toxemia	Status on Discharge
			Ad.	Av.					
108	26	M	120	130	70	98.6	N	—	Arrested
109	25	M	125	160	90	100.5	N	++	Improved
110	37	M	120	125	100	100.0	N	++	Progressive
111	26	M	124	150	90	99.2	N	+	Arrested
112	32	M	125	150	100	100.0	N	++	App. Cured
113	30	F	128	128	85	98.6	N	—	Arrested
114	33	M	125	140	85	98.6	N	—	Arrested
115	21	M	120	145	90	99.0	N	+	Arrested
116	28	M	100	100	120	101.0	Casts	+++	Progressive
117	28	M	130	135	80	98.6	N	—	Arrested
118	23	M	120	130	74	99.0	N	+	Improved
119	23	F	110	135	90	98.6	N	—	App. Cured
120	26	M	132	145	85	98.6	N	—	Arrested
121	17	M	100	125	100	99.0	N	+	Arrested
122	23	M	118	135	90	99.4	N	+	Improved
123	21	M	125	150	90	99.6	N	+	Arrested
124	28	M	115	150	80	98.6	N	—	App. Cured
125	29	M	118	135	85	99.0	N	+	Improved
126	32	F	125	145	100	99.0	N	+	Arrested
127	24	M	130	150	75	98.6	N	—	App. Cured
128	36	M	135	140	80	98.6	N	—	Arrested
129	30	F	110	135	96	99.2	N	+	Arrested
130	21	F	110	135	90	98.6	N	—	App. Cured
131	40	F	116	136	100	99.4	N	+	Arrested
132	24	F	130	134	96	98.6	N	—	App. Cured
133	15	F	114	135	96	98.6	N	—	App. Cured
134	21	M	145	148	80	98.6	N	--	Arrested
135	44	M	150	130	100	99.5	N	+	Progressive
136	21	M	140	155	120	99.2	N	+	Improved
137	32	M	115	138	90	99.0	N	+	Arrested
138	39	M	130	105	100	99.4	N	+	Progressive
139	38	M	140	160	80	99.0	N	+	App. Cured
140	35	M	130	145	100	99.2	N	+	Improved
141	33	M	140	140	100	100.0	Alb.	++	Unimproved
142	56	M	140	150	80	98.6	N	—	Improved
143	37	M	130	145	88	98.6	N	—	App. Cured
144	58	M	185	165	120	98.6	Alb.	—	Progressive
145	44	F	133	135	88	98.6	N	—	App. Cured
146	25	F	115	125	90	100.0	N	++	Improved
147	29	M	130	140	80	98.6	N	—	App. Cured
148	22	M	142	155	76	98.6	N	—	App. Cured
149	27	M	135	125	90	99.2	N	+	Unimproved
150	55	M	160	160	80	98.6	N	—	Arrested
151	25	M	100	115	86	100.0	N	++	Arrested
152	36	M	135	120	100	100.0	N	++	Progressive
153	24	M	140	112	120	99.4	N	+	Progressive
154	30	M	125	130	76	98.6	N	—	App. Cured
155	19	M	120	130	88	99.6	N	+	Arrested
156	35	M	120	130	100	99.2	N	+	Improved
157	26	M	120	140	90	98.6	N	—	App. Cured
158	26	M	120	110	100	99.4	N	+	Arrested
159	36	M	115	130	100	99.0	N	+	Improved
160	26	M	110	88	120	101.0	N	+++	Died
161	30	F	130	120	95	100.0	N	++	Progressive
162	30	M	120	120	85	98.6	N	—	App. Cured

TABLE 1.—DATA CONCERNING SIX HUNDRED CONSUMPTIVES—(Continued)

Case No.	Age	Sex	Blood Pressure		Pulse Av.	Temp. F. Av.	Urine	Degree of Toxemia	Status on Discharge
			Ad.	Av.					
163	26	M	110	130	90	99.4	N	+	Improved
164	23	M	104	130	100	99.6	N	+	Arrested
165	32	F	113	130	95	99.2	N	+	App. Cured
166	22	M	105	120	90	98.6	N	—	Arrested
167	22	M	100	130	90	99.6	N	+	Improved
168	45	F	95	136	85	98.6	N	—	Arrested
169	19	F	110	120	80	98.6	N	—	Improved
170	25	M	94	125	100	98.6	N	—	Improved
171	32	F	103	125	90	98.6	N	—	App. Cured
172	29	M	126	130	95	99.4	N	+	Improved
173	25	F	100	126	100	99.0	N	+	Improved
174	40	F	120	135	85	98.6	N	—	Arrested
175	25	M	122	138	85	98.6	N	—	App. Cured
176	48	F	135	135	90	98.6	N	—	App. Cured
177	29	M	138	138	100	99.4	N	+	Improved
178	26	M	124	130	120	100.0	N	++	.....‡
179	31	M	120	115	100	100.0	N	++	.....†
180	36	F	146	146	100	99.2	N	+	Improved§
181	40	M	150	138	90	99.6	Sugar	+	Improved
182	26	M	128	132	85	98.6	N	—	App. Cured
183	37	M	124	135	85	99.2	N	+	Improved
184	18	M	122	135	75	98.6	N	—	App. Cured
185	22	M	140	140	120	99.2	N	+	Unimproved
186	34	M	134	118	100	99.4	N	+	Progressive
187	20	M	134	145	90	99.0	N	+	Improved
188	24	F	110	118	90	99.6	N	+	Improved
189	18	F	118	118	100	99.4	N	+	Progressive
190	27	M	116	145	90	99.8	N	+	Progressive¶
191	35	F	130	125	90	99.0	N	+	Improved
192	35	M	125	140	90	98.6	N	—	Arrested
193	23	M	116	116	120	101.0	N	+++	Progressive
194	24	F	130	130	90	98.6	N	—	App. Cured
195	20	M	142	142	90	98.6	N	—	App. Cured
196	43	F	105	128	90	98.6	N	—	App. Cured
197	42	M	126	138	85	98.6	N	—	Arrested
198	27	M	138	145	84	98.6	N	—	.....†
199	32	F	132	126	100	100.0	N	++	.....†
200	18	F	126	126	80	98.6	N	—	Arrested
201	28	M	125	125	110	99.6	N	+	Unimproved
202	25	M	132	130	85	98.6	N	—	Improved
203	36	M	176	150	80	99.0	N	+	Arrested‖
204	25	M	132	145	90	98.6	N	—	Arrested
205	26	M	132	130	85	98.6	N	—	App. Cured
206	19	M	122	110	120	101.0	N	+++	Progressive
207	33	M	110	120	100	99.4	N	+	Improved
208	26	M	124	120	80	100.0	N	++	Progressive
209	20	M	108	135	85	99.0	N	+	Improved
210	25	M	120	123	75	98.6	N	—	App. Cured
211	28	F	90	108	100	98.6	N	—	Arrested
212	26	M	105	120	100	99.6	N	+	Improved
213	20	M	105	100	90	100.0	N	++	Progressive

‡ Died suddenly. Acute dilatation of heart.
§ Sugar responsible for high blood-pressure.
¶ Hemorrhage case. High blood-pressure due to this.
‖ Alcoholic.

TABLE 1. — DATA CONCERNING SIX HUNDRED CONSUMPTIVES — (Continued)

Case No.	Age	Sex	Blood Pressure		Pulse Av.	Temp. F. Av.	Urine	Degree of Toxemia	Status on Discharge
			Ad.	Av.					
214	38	M	133	145	80	98.6	N	—	Arrested
215	17	F	122	127	85	98.6	N	—	App. Cured
216	27	M	118	130	85	98.6	N	—	Arrested
217	28	M	110	123	80	98.6	N	—	App. Cured
218	30	F	105	120	80	98.6	N	—	Arrested
219	21	M	110	120	100	98.6	Trace Alb.	—	Improved
220	39	F	110	135	100	99.4	N	+	Improved
221	32	F	95	97	98	98.6	N	—	Arrested
222	20	F	126	127	75	99.0	N	+	Arrested
223	30	F	120	124	90	98.6	N	—	Arrested
224	27	F	100	108	100	99.6	N	+	.....†
225	40	M	120	145	100	98.6	N	—	Arrested
226	21	M	120	124	90	98.6	N	—	Improved
227	47	M	118	140	95	99.0	N	+	Arrested
228	33	M	120	120	90	98.6	N	—	Arrested
229	60	F	115	145	100	98.6	N	—	App. Cured
230	30	M	120	148	80	98.6	N	—	Arrested
231	19	M	120	130	90	98.6	N	—	Arrested
232	18	M	107	118	95	100.0	N	++	Progressive
233	25	M	125	133	85	98.6	N	—	Arrested
234	25	M	110	110	95	100.0	N	++	Improved
235	27	F	120	120	90	98.6	N	—	Arrested
236	24	M	122	127	85	98.6	N	—	App. Cured
237	18	M	125	138	100	99.0	N	+	Improved
238	39	M	115	130	100	99.0	N	+	Unimproved
239	23	M	120	120	100	99.0	N	+	Improved
240	41	F	100	115	100	101.0	N	+++	Improved
241	26	F	115	125	75	98.6	N	—	App. Cured
242	36	M	124	115	88	99.6	N	+	Progressive
243	29	M	122	138	90	99.0	N	+	Improved
244	36	M	122	123	90	99.0	N	+	Improved
245	24	F	128	130	90	99.0	N	+	Improved
246	26	M	115	125	80	98.6	N	—	App. Cured
247	29	M	100	100	120	100.0	N	++	Progressive
248	41	M	122	112	120	100.0	N	++	Progressive
249	20	F	110	115	100	98.6	N	—	App. Cured
250	39	M	128	130	80	98.6	N	—	App. Cured
251	32	M	130	135	85	98.6	N	—	Arrested
252	36	M	118	110	120	100.0	N	++	Progressive
253	57	M	132	140	110	100.0	Alb.	++	Progressive
254	22	M	110	118	110	98.6	N	—	App. Cured
255	44	M	105	120	85	99.0	Alb.	+	Arrested
256	39	F	120	120	90	98.6	N	—	Improved
257	35	F	102	112	90	98.6	N	—	Improved
258	28	F	110	114	..	98.6	N	—	App. Cured
259	49	M	110	120	80	99.6	N	+	Improved
260	42	M	123	126	95	98.6	N	—	Arrested
261	39	M	120	125	80	98.6	N	—	App. Cured
262	23	M	117	119	85	98.6	N	—	Arrested
263	22	M	130	115	100	99.8	N	+	Progressive
264	29	F	130	130	80	98.6	N	—	App. Cured
265	48	M	135	138	80	98.6	N	—	App. Cured
266	31	M	104	115	90	99.6	N	+	Improved
267	32	M	124	150	90	98.6	N	—	Arrested
268	26	M	125	118	110	100.0	N	++	Progressive

TABLE 1. — DATA CONCERNING SIX HUNDRED CONSUMPTIVES — (Continued)

Case No.	Age	Sex	Blood Pressure		Pulse Av.	Temp. F. Av.	Urine	Degree of Toxemia	Status on Discharge
			Ad.	Av.					
269	22	M	122	130	100	99.0	N	+	Improved
270	29	M	125	128	..	98.6	N	—	App. Cured
271	38	M	124	124	120	100.4	N	++	Progressive
272	20	F	120	120	90	99.0	N	+	Unimproved
273	35	F	155	160	95	99.6	N	+	App. Cured
274	25	F	125	126	80	98.6	N	—	App. Cured
275	43	F	125	125	90	98.6	N	—	Unimproved
276	44	M	122	135	..	98.6	N	—	App. Cured
277	33	M	125	140	90	98.6	N	—	App. Cured
278	25	M	128	135	80	98.6	N	—	Improved
279	30	F	125	125	85	98.6	N	—	Unimproved
280	43	M	126	127	85	99.0	N	+	Unimproved
281	47	F	103	125	100	99.4	N	+	Arrested
282	26	M	118	119	90	99.4	N	+	Unimproved
283	42	F	108	105	120	100.0	N	++	Progressive
284	42	F	120	125	100	98.6	N	—	Improved
285	22	F	118	120	95	98.6	N	—	Arrested
286	33	M	110	123	105	99.0	N	+	Arrested
287	22	M	125	125	90	99.4	Trace Alb.	+	Unimproved
288	23	F	98	123	90	98.6	N	—	Arrested
289	21	M	115	112	120	102.0	N	+++	Progressive
290	26	F	98	118	110	99.0	N	+	Arrested
291	19	M	112	112	130	99.6	N	+	Progressive
292	22	M	123	120	120	101.0	N	+++	Progressive**
293	20	M	108	115	95	99.0	N	+	Progressive
294	37	M	122	112	110	100.0	N	++	Progressive
295	6	F	90	100	90	99.0	N	+	App. Cured††
296	31	M	135	138	95	98.6	N	—	Improved
297	40	M	130	135	85	98.6	N	—	Arrested
298	40	F	137	137	85	99.0	N	+	Unimproved
299	23	M	116	115	90	99.0	N	+	Unimproved
300	36	M	134	145	80	98.6	N	—	App. Cured
301	42	F	110	110	120	99.2	Alb. Casts	+	Progressive
302	18	F	128	135	80	99.0	N	+	App. Cured
303	32	M	115	112	90	Nor.	N	—	Arrested
304	35	M	130	140	100	Nor.	N	—	Arrested
305	30	F	125	125	85	Nor.	N	—	App. Cured
306	35	M	120	130	90	99.0	N	+	Arrested
307	22	M	100	120	90	Nor.	N	—	App. Cured
308	22	M	105	125	95	Nor.	N	—	App. Cured
309	22	M	100	125	90	Nor.	N	—	Arrested
310	32	F	103	120	90	Nor.	N	—	App. Cured
311	25	F	100	120	100	Nor.	N	—	Improved
312	24	F	95	115	90	99.2	Alb. Casts	+	App .Cured
313	26	F	105	110	130	102.0	Casts	+++	Progressive
314	19	M	130	140	90	Nor.	Casts	—	App. Cured‡‡
315	33	M	137	140	80	Nor.	N	—	App. Cured
316	39	F	100	125	90	Nor.	N	—	Arrested
317	23	M	110	130	95	99.2	N	+	Improved
318	18	M	107	107	90	99.3	N	+	Stationary
319	45	M	125	115	90	99.2	N	+	Progressive
320	20	F	115	120	96	99.0	N	+	Improved

** Blood-pressure not taken toward end of treatment.

†† Joint case.

‡‡ Urine normal on discharge.

TABLE 1. — DATA CONCERNING SIX HUNDRED CONSUMPTIVES — (Continued)

Case No.	Age	Sex	Blood Pressure		Pulse Av.	Temp. F. Av.	Urine	Degree of Toxemia	Status on Discharge
			Ad.	Av.					
321	21	M	152	160	85	Nor.	N	—	Arrested
322	33	M	128	145	100	99.3	N	+	Improved
323	34	M	124	127	90	Nor.	N	—	Improved
324	25	F	100	125	80	Nor.	N	—	App. Cured
325	27	M	130	140	85	Nor.	N	—	Arrested
326	26	M	138	140	85	Nor.	N	—	App. Cured
327	41	M	104	125	90	99.2	N	+	Improved
328	35	M	104	117	90	99.0	N	—	Died§§
329	47	F	148	145	100	100.0	N	++	Progressive
330	33	M	150	145	80	99.0	N	+	Arrested
331	26	M	134	142	80	Nor.	N	—	App. Cured
332	34	F	105	110	88	100.0	N	++	Improved
333	30	M	128	134	80	Nor.	N	—	App. Cured
334	36	M	134	140	80	Nor.	N	—	App. Cured
335	30	M	114	120	100	100.4	N	++	Improved
336	21	M	104	134	85	Nor.	N	—	Arrested
337	32	F	135	135	90	99.4	N	+	Arrested
338	27	M	125	128	88	Nor.	N	—	App. Cured
339	24	F	98	90	120	100.0	N	++	Progressive
340	22	M	120	124	85	Nor.	N	—	App. Cured
341	23	M	100	130	90	Nor.	N	+	App. Cured
342	45	F	145	150	90	99.0	N	+	Arrested
343	18	F	120	125	80	99.0	N	+	App. Cured
344	29	M	124	145	72	99.0	N	—	Improved
345	25	M	138	150	90	Nor.	N	—	Arrested
346	51	M	128	144	90	Nor.	N	—	Improved
347	32	F	120	135	80	Nor.	N	—	App. Cured
348	18	F	115	125	85	Nor.	N	—	App. Cured
349	21	M	124	140	120	99.4	N	+	Improved
350	32	F	100	138	85	Nor.	N	—	Arrested
351	30	M	140	144	80	Nor.	N	—	App. Cured
352	32	M	124	134	80	Nor.	N	—	App. Cured
353	25	F	130	136	80	Nor.	N	—	Arrested
354	45	M	154	154	100	99.0	N	+	Stationary
355	24	M	144	154	90	Nor.	N	—	Arrested
356	31	M	144	150	75	Nor.	N	—	App. Cured
357	39	M	145	126	125	99.3	N	+	Progressive
358	23	M	128	150	75	Nor.	N	—	App. Cured
359	23	M	115	140	80	Nor.	N	—	App. Cured
360	22	M	122	130	80	Nor.	N	—	App. Cured
361	22	F	100	118	80	Nor.	N	—	App. Cured
362	18	M	140	144	80	Nor.	N	—	Arrested
363	32	M	120	140	85	Nor.	N	—	Arrested
364	34	F	124	135	95	Nor.	N	—	Improved
365	24	F	128	135	85	Nor.	N	—	App. Cured
366	22	F	118	124	72	Nor.	N	—	App. Cured
367	39	F	114	120	90	Nor.	N	—	Arrested
368	23	F	120	120	100	100.0	N	++	Progressive
369	24	M	108	125	95	Nor.	N	—	Improved
370	28	M	150	160	72	Nor.	N	—	App. Cured
371	19	M	146	146	72	Nor.	N	—	App. Cured
372	41	F	135	140	80	Nor.	N	—	App. Cured
373	28	M	114	125	90	100.0	N	++	Improved
374	31	F	124	135	90	99.0	N	+	Improved
375	20	M	122	150	100	99.0	N	+	Improved
376	22	M	110	135	95	99.2	N	+	Improved

§§ Sudden hemorrhage.

TABLE 1. — DATA CONCERNING SIX HUNDRED CONSUMPTIVES — (Continued)

Case No.	Age	Sex	Blood Pressure		Pulse Av.	Temp. F. Av.	Urine	Degree of Toxemia	Status on Discharge
			Ad.	Av.					
377	25	M	128	150	95	Nor.	N	—	Improved
378	40	F	128	128	100	100.0	N	++	Stationary
379	32	M	134	110	90	99.4	N	+	Progressive
380	22	F	116	125	78	99.0	N	+	Improved
381	25	M	110	125	85	Nor.	N	—	Improved
382	28	M	138	150	100	Nor.	N	—	Improved
383	35	M	124	140	90	Nor.	N	—	Improved
384	44	F	98	115	90	Nor.	N	—	Improved
385	23	M	116	135	85	99.0	N	+	Improved
386	23	M	145	145	90	99.0	N	+	Improved
387	27	M	126	130	100	99.2	N	+	Improved
388	25	M	134	140	85	Nor.	N	—	Arrested
389	29	F	114	125	90	Nor.	N	—	Improved
390	24	M	116	125	95	99.0	N	+	Improved
391	31	F	135	140	80	Nor.	N	—	App. Cured
392	20	M	148	135	85	Nor.	Alb. Casts	—	Improved¶¶
393	23	M	100	128	72	Nor.	N	—	Arrested
394	21	M	145	145	85	Nor.	N	—	Improved
395	25	M	150	150	72	Nor.	N	—	Improved
396	27	M	146	150	72	Nor.	N	—	Improved
397	38	M	130	135	70	Nor.	N	—	Improved
398	18	M	104	115	110	100.0	N	++	Stationary
399	39	M	125	138	90	Nor.	N	—	Improved
400	29	F	115	110	90	101.0	N	+++	Stationary
401	29	F	135	140	78	Nor.	N	—	Arrested
402	29	M	148	148	80	Nor.	N	—	Improved
403	31	M	124	130	80	Nor.	N	—	Improved
404	30	F	120	130	90	99.3	N	+	Improved
405	24	F	118	122	90	99.0	N	+	Improved
406	20	M	126	135	90	Nor.	N	—	Arrested
407	23	F	130	135	90	99.0	N	+	Improved
408	35	M	145	155	80	Nor.	N	+	Arrested
409	23	M	134	150	85	99.0	N	+	Improved
410	19	M	144	160	85	Nor.	N	—	Arrested
411	26	M	132	140	100	99.1	N	+	Improved
412	36	M	176	188	90	Nor.	N	—	App. Cured‖‖
413	41	F	128	136	85	99.4	N	+	Improved
414	33	F	124	140	90	Nor.	N	—	Arrested
415	45	M	136	150	72	99.2	N	+	Improved
416	35	M	180	190	90	Nor.	N	—	Arrested
417	33	M	166	170	90	Nor.	N	—	Improved
418	28	M	140	140	72	Nor.	N	—	Arrested
419	21	M	138	142	72	Nor.	N	—	Improved
420	28	M	146	148	90	99.0	N	+	Improved
421	38	M	132	126	120	101.0	N	++	Progressive
422	45	M	148	140	95	99.0	N	+	Stationary
423	40	M	148	148	80	Nor.	N	—	Stationary
424	25	F	128	140	90	99.0	N	+	Improved
425	22	M	130	152	95	99.1	Alb. Casts	+	Improved
426	20	M	150	150	100	99.3	N	+	Stationary
427	41	M	152	146	90	Nor.	N	—	Improved
428	21	F	114	138	95	99.0	N	+	App. Cured
429	40	F	140	148	80	Nor.	N	—	App. Cured
430	22	M	160	150	120	99.0	N	+	Progressive

¶¶ Removal of tuberculous testicle.
‖‖ Hard drinker.

TABLE 1. — DATA CONCERNING SIX HUNDRED CONSUMPTIVES — (Continued)

Case No.	Age	Sex	Blood Pressure		Pulse Av.	Temp. F. Av.	Urine	Degree of Toxemia	Status on Discharge
			Ad.	Av.					
431	35	M	134	138	100	99.0	N	+	Stationary
432	29	M	138	138	85	Nor.	N	—	Improved
433	28	F	160	154	90	99.0	N	+	Improved
434	27	M	134	145	112	99.2	N	+	Improved
435	21	M	140	148	105	Nor.	N	—	Improved
436	26	M	148	160	80	Nor.	N	—	Arrested
437	20	M	145	136	72	Nor.	N	—	Arrested
438	33	F	122	148	90	99.0	N	+	Arrested
439	30	F	140	140	80	Nor.	N	—	Cured
440	20	M	132	136	100	100.3	Alb. Casts	++	Died†
441	25	M	120	140	120	99.2	N	+	Stationary
442	30	M	134	145	85	Nor.	N	—	Arrested
443	37	M	136	148	85	99.1	N	+	Cured
444	30	M	160	127	120	101.0	N	++	Progressive
445	30	M	150	155	85	Nor.	N	—	Arrested
446	27	M	118	125	100	99.0	N	+	Improved
447	31	F	134	140	90	99.2	N	+	Arrested
448	20	M	178	165	80	Nor.	N	—	Arrested
449	28	F	130	145	95	99.2	N	+	Improved
450	44	M	132	140	90	99.2	N	+	Improved
451	49	M	150	150	85	Nor.	N	—	Arrested
452	54	M	140	175	90	99.0	N	+	Arrested
453	33	M	148	155	72	Nor.	N	—	Arrested
454	24	M	175	175	85	Nor.	N	—	Arrested
455	33	M	130	140	80	Nor.	N	—	App. Cured
456	19	M	140	155	85	99.0	N	+	Arrested
457	27	M	130	126	100	99.3	N	+	Progressive
458	36	M	138	138	95	99.0	N	+	Arrested
459	58	M	122	122	130	101.0	N	++	Progressive
460	26	M	150	150	80	99.0	N	+	App. Cured
461	23	M	110	135	90	99.0	N	+	Improved
462	23	M	130	125	95	99.3	N	+	Progressive
463	33	M	136	145	100	Nor.	N	—	Arrested
464	22	M	128	145	85	Nor.	N	—	App. Cured
465	21	M	122	146	80	Nor.	N	—	Arrested
466	26	M	140	160	85	Nor.	N	—	Arrested
467	24	M	132	145	90	99.2	N	+	Improved
468	51	F	142	148	80	Nor.	N	—	App. Cured
469	30	M	130	135	90	Nor.	N	—	Improved
470	37	M	142	146	90	Nor.	N	—	Arrested
471	21	M	130	140	100	100.0	N	+	Improved
472	22	M	128	135	100	99.0	N	+	Improved
473	38	M	144	148	110	100.0	Sug. & Alb.	+	Prog'sive***
474	26	M	140	150	80	Nor.	N	—	Arrested
475	22	F	130	135	100	Nor.	N	—	Arrested
476	26	M	132	140	85	99.0	N	+	App. Cured
477	38	M	142	155	85	Nor.	N	—	App. Cured
478	30	M	114	126	80	99.2	N	+	Improved
479	25	M	140	140	90	Nor.	N	—	Arrested
480	39	M	128	136	100	99.4	N	+	Improved
481	37	M	140	142	85	Nor.	N	—	Arrested
482	17	M	142	148	90	99.0	N	+	Arrested
483	23	M	100	100	120	101.0	Alb. Casts	++	Progressive
484	27	M	150	150	90	Nor.	N	—	Arrested
485	20	F	138	140	85	99.0	N	+	Arrested

*** Kidney case.

TABLE 1. — DATA CONCERNING SIX HUNDRED CONSUMPTIVES — (Continued)

Case No.	Age	Sex	Blood Pressure		Pulse Av.	Temp. F. Av.	Urine	Degree of Toxemia	Status on Discharge
			Ad.	Av.					
486	50	M	110	120	100	100.0	N	+	Improved
487	23	M	146	155	85	Nor.	N	—	Arrested
488	27	M	118	135	80	Nor.	N	—	Arrested
489	21	F	130	135	100	99.2	N	+	Improved
490	18	F	140	140	100	99.2	N	+	Improved
491	24	M	122	145	72	Nor.	N	—	App. Cured
492	26	M	145	145	90	Nor.	N	—	Arrested
493	46	M	160	155	90	99.2	N	+	Progressive
494	44	M	122	140	100	Nor.	N	—	Arrested
495	26	M	118	95	110	100.2	N	++	Progressive
496	33	M	106	120	100	99.4	N	+	Improved
497	32	M	116	130	100	99.2	N	+	Improved
498	26	M	130	120	100	100.0	N	+	Progressive
499	27	M	142	142	90	Nor.	N	—	Cured
500	26	M	136	144	95	Nor.	N	—	Arrested
501	33	M	112	106	120	100.0	N	+	Progressive
502	24	F	128	128	120	101.0	N	++	Progressive
503	36	M	142	145	90	99.4	N	+	Improved
504	26	M	150	150	80	Nor.	N	—	Arrested
505	50	M	100	130	90	Nor.	N	—	Arrested
506	30	F	130	150	90	Nor.	N	—	Arrested
507	29	M	136	140	90	Nor.	N	—	Improved
508	26	M	126	135	72	Nor.	N	—	Improved
509	19	F	124	124	90	Nor.	N	—	Improved
510	22	M	127	138	90	Nor.	N	—	Improved
511	30	F	130	112	100	100.0	N	+	Progressive
512	27	F	145	150	85	Nor.	N	—	Improved
513	22	F	132	135	85	99.0	N	+	Improved
514	25	M	125	125	72	Nor.	N	—	Stationary
515	34	F	125	130	90	99.2	N	+	Arrested
516	22	M	124	145	90	99.0	N	+	Arrested
517	43	M	100	140	90	99.4	N	+	Improved
518	34	M	134	144	85	Nor.	N	—	App. Cured
519	35	F	110	130	90	Nor.	N	—	Arrested
520	23	F	132	138	80	Nor.	N	—	Improved
521	36	M	150	155	90	Nor.	N	—	Improved
522	30	M	126	128	90	Nor.	N	—	Improved.
523	24	M	125	125	90	Nor.	N	—	Stationary
524	40	F	135	140	80	99.2	N	+	Arrested
525	29	F	125	130	90	99.0	N	+	Improved
526	34	M	138	145	80	Nor.	N	—	Arrested
527	22	M	135	145	85	Nor.	N	—	Improved
528	33	M	134	150	72	Nor.	N	—	Improved
529	27	M	124	135	90	Nor.	N	—	Arrested
530	24	F	116	125	90	Nor.	N	—	Improved
531	32	F	120	125	85	99.2	N	+	Improved
532	51	M	125	140	90	Nor.	N	—	Improved
533	29	M	134	140	90	Nor.	N	—	Arrested
534	29	M	130	145	80	Nor.	N	—	Improved
535	25	M	130	140	85	Nor.	N	—	Arrested
536	18	F	128	128	80	Nor.	N	—	Stationary
537	35	M	150	150	72	Nor.	N	—	Improved
538	20	F	115	140	100	Nor.	N	—	Improved
539	25	M	135	135	80	Nor.	N	—	Improved
540	38	M	150	150	72	99.2	N	+	Improved
541	30	F	100	135	72	Nor.	N	—	App. Cured
542	33	F	100	135	90	Nor.	N	—	Arrested

Case No.	Age	Sex	Blood Pressure		Pulse Av.	Temp. F. Av.	Urine	Degree of Toxemia	Status on Discharge
			Ad.	Av.					
1	30	F	128	136	84	Nor.	N	—	Arrested
2	42	M	135	145	82	Nor.	N	—	Arrested
3	28	M	114	110	98	100.0	N	+	Stationary
4	27	M	132	134	78	Nor.	N	—	Arrested
5	28	M	120	128	77	Nor.	N	—	Arrested
6	51	M	106	115	86	Nor.	N	—	Improved
7	24	M	130	136	80	Nor.	N	—	Arrested
8	67	F	116	120	86	99.2	N	+	Improved
9	27	M	110	128	80	99.0	N	+	Arrested†††
10	35	F	118	130	74	Nor.	N	—	Arrested
11	34	F	136	130	70	Nor.	N	—	Arrested
12	26	F	120	124	90	99.0	N	+	Improved
13	39	M	138	140	58	Nor.	N	—	Arrested
14	24	M	122	136	76	99.2	N	+	Improved
15	26	M	112	138	84	Nor.	N	—	Arrested
16	23	F	128	126	90	99.0	N	+	Improved
17	26	M	114	132	84	Nor.	N	—	Arrested‡‡‡
18	30	M	122	130	54	Nor.	N	—	Arrested
19	27	F	124	132	80	Nor.	N	—	Arrested
20	25	F	126	134	82	Nor.	N	—	Arrested
21	45	F	145	152	76	Nor.	N	—	Arrested
22	26	M	125	140	80	99.0	N	+	Arrested
23	45	F	140	150	76	Nor.	N	—	Arrested
24	28	M	130	134	80	Nor.	N	—	Arrested
25	27	M	138	146	80	Nor.	N	—	Arrested
26	24	F	122	134	76	Nor.	N	—	Arrested
27	23	F	106	114	82	Nor.	N	—	Arrested§§§
28	29	M	122	132	80	Nor.	N	—	Arrested
29	30	F	122	134	76	Nor.	N	—	Arrested
30	28	F	118	130	82	99.2	N	+	Arrested
31	41	M	138	138	74	Nor.	N	—	Arrested
32	24	M	112	124	80	Nor.	N	—	Arrested
33	34	F	128	132	86	Nor.	N	—	Arrested
34	29	M	134	136	94	99.4	N	+	Stationary
35	27	M	140	150	72	Nor.	N	—	Arrested
36	24	M	114	130	70	Nor.	N	—	Arrested
37	29	M	126	134	68	Nor.	N	—	Arrested
38	30	M	120	128	74	Nor.	N	—	Arrested
39	27	M	145	140	74	Nor.	Alb.	—	Arrested
40	35	M	128	134	78	Nor.	N	—	Arrested
41	23	F	118	130	84	Nor.	N	—	Arrested
42	25	F	110	126	86	Nor.	N	—	Arrested
43	32	M	126	140	84	Nor.	N	—	Arrested
44	28	M	120	120	100	94.4	N	+	Stationary
45	31	M	110	134	90	Nor.	N	—	Improved
46	36	M	118	136	80	Nor.	N	—	Arrested
47	24	M	112	136	70	Nor.	N	—	Arrested
48	26	F	108	124	76	99.4	N	+	Arrested
49	28	M	117	132	90	100.0	N	+	Improved
50	30	M	110	120	55	Nor.	N	—	Arrested
51	30	F	120	132	88	Nor.	N	—	Improved
52	30	F	104	110	112	101.2	N	++	Improved
53	36	F	118	138	74	Nor.	N	—	Arrested
54	29	F	120	132	86	Nor.	N	—	Arrested
55	25	F	116	136	86	Nor.	N	—	Arrested
56	16	M	118	126	80	99.2	N	+	Improved
57	31	M	120	136	76	Nor.	N	—	Arrested
58	37	M	128	144	84	99.0	N	+	Improved

††† Tuberculosis of the intestines. ‡‡‡ Hemorrhage. §§§ Mitral stenosis.

changed little from that day to this. But there existed no scientific fact for such belief. It remained for altitude workers of later years to determine the factors that favorably influenced the course of the disease. And in a careful study of these observations one is forced to the conclusion that altitude is the chief element in the question of climate. As proof of this statement we would cite you the excellent work of Williams[14] of London on the marked expansion of the thorax with greater amount of oxygen content in the blood; the work of Webb and Williams[15] of

TABLE 2.—Blood-Pressure Data Concerning Fifty Males. Normal Individuals

Case No.	Age	Blood Pressure	Case No.	Age	Blood Pressure
1	51	142	26	25	135
2	29	144	27	23	116
3	36	145	28	23	116
4	25	152	29	44	148
5	30	138	30	55	175
6	66	125	31	27	154
7	22	142	32	23	135
8	28	154	33	21	162
9	54	134	34	21	152
10	42	116	35	21	138
11	52	165	36	28	125
12	31	130	37	28	155
13	36	154	38	21	154
14	52	154	39	28	150
15	27	164	40	21	140
16	50	170	41	21	135
17	46	150	42	37	170
18	38	122	43	37	125
19	19	136	44	43	135
20	30	162	45	35	150
21	43	144	46	48	125
22	38	134	47	55	148
23	35	132	48	41	140
24	22	120	49	38	154
25	34	150	50	43	148

Colorado Springs showing a marked lymphocytosis in altitude; and the painstaking experiments of the English Commission,[16] working with American collaborators, showing over a 40 per cent. increase in erythrocytes and proving beyond doubt that the increased hemoglobin content of the blood was not relative but actual.

Now, granting with Emerson,[11] that the result of hypotension in tuberculosis, or in any other condition, is insufficient capillary pressure,

14. Williams: Trans. Internat. Cong. Tub., 1908.
15. Webb and Williams: Trans. Nat. Assn. for Study and Prev. Tub., 1909.
16. Douglas and Haldane, Schneider and Henderson: Physiological Experiments on Pike's Peak, Summer, 1910.

more or less venous stagnation, and insufficient nourishment with resulting atrophy and degeneration of the essential organs of the body, why then, we ask, if our work is confirmed by other observers, is this factor of increased blood-pressure at high altitude not an essential element in the treatment of all forms of tuberculosis? We feel from our own standpoint that we have shown conclusively that such an increase occurs and we now await with interest a confirmation or a refutation of our work by competent observers.

TABLE 3.—DATA REGARDING BLOOD-PRESSURE IN TREATED PATIENTS

Average blood-pressure on admission in 542 cases	124
Average blood-pressure during treatment in 542 cases	132
Average increase	8
Number of cures	110
Average pressure on admission	124
Average pressure during treatment	135
Average increase	11
Number arrested	153
Average pressure on admission	125
Average pressure during treatment	137
Average increase	12
Number improved	171
Average pressure on admission	123
Average pressure during treatment	133
Average increase	10
Number stationary	36
Average pressure on admission	130
Average pressure during treatment	130
Average increase	0

NOTE.—The high average pressure here is due to two kidney cases with pressures of 164 and 148, which taken out, gives an admission average of 128 and a treatment average of 129, with increase of 1.

Number of progressives	59
Average pressure on admission	122
Average pressure during treatment	115
Average decrease	7

We give here a table of six hundred cases (Table 1). We are indebted to Dr. O. T. Hyde of St. Joseph's Sanatorium, Silver City, N. M., for the Faught records of fifty cases (Table 2). To eliminate the personal equation we also append a table (Table 5) showing a comparison of the readings on a Stanton and an Erlanger. In the entire series of cases we have used at different times a Janeway, a Stanton and a Faught. In all readings the cuff was applied to the left arm above the elbow, the patient in a sitting posture, the forearm flexed on a line with the heart. The systolic pressure alone was recorded since for all practical purposes we feel that this is sufficient, and also, we do not believe that an accurate diastolic reading can be made with an ordinary

instrument. The observations were made between the hours of nine and ten in the morning as nearly as this was possible in our routine work. The blood-pressure is given on admission, as is also the average for the time under observation, this time being about seven months. In recording the pulse and temperature we have taken an average during the stay at the sanatorium. The degree of toxemia is represented as follows: — = a normal temperature; + = 99 to 100; ++ = 100 to 101; +++ = 101 and over. It is interesting to note that the averages of Dr. Hyde's cases taken independently of our own work shows an average on admission of but two points lower than our own and exactly the same average during treatment, and an analysis of his cases proves the points brought out by the analysis of our own table.

TABLE 4.—RELATION BETWEEN TOXEMIA AND BLOOD-PRESSURE

Number of cases with minus toxemia	300
Average pulse	85
Average blood-pressure	124
Number of cases with plus toxemia	184
Average pulse	72
Average blood-pressure	132
Number of cases with two plus toxemia	46
Average pulse	105
Average blood-pressure	120
Number of cases with three plus toxemia	11
Average pulse	115
Average blood-pressure	111

A detailed study of the facts noted in the general column shows some interesting relations which are grouped separately (Table 3).

From a study of the tables referred to we find that in all cases showing a betterment in pulmonary condition we get an increase in blood-pressure; in all cases showing no improvement we find the pressure practically the same; in all showing a progressive tendency we find a decrease in blood-pressure.

Classifying the minus and plus degree of toxemia as a class showing practically no toxic absorption, we find that the average pulse is 78, and the average pressure 128. Then further combining the two plus and three plus toxemia as a class showing marked toxic absorption, we find the average pulse to be 110 and the average blood-pressure to be 115. Here is shown the inverse ratio of pulse and blood-pressure, namely, the higher the pulse, the lower the blood-pressure, and *vice versa*. It also shows clearly that the greater the degree of toxemia the lower the blood-pressure, and the less the degree of toxemia the higher the blood-pressure.

As has been previously stated, pressures were taken with the Stanton and Erlanger apparatus during the same sitting in order to determine the comparative value of the cheaper instruments. We here append a table of forty cases showing this comparison (Table 5).

TABLE 5.—Comparison of Blood-Pressures Taken with Stanton and Erlanger Instruments

	Erlanger	Stanton
1	115	114
2	145	140
3	130	124
4	124	120
5	128	124
6	122	125
7	148	146
8	126	126
9	128	128
10	110	110
11	114	114
12	164	164
13	134	134
14	128	132
15	136	135
16	148	144
17	130	124
18	142	136
19	138	138
20	112	114
21	126	126
22	136	136
23	134	136
24	116	116
25	132	130
26	134	134
27	120	122
28	132	134
29	124	124
30	132	134
31	124	124
32	120	122
33	116	116
34	144	142
35	138	138
36	132	130
37	110	110
38	124	122
39	128	126
40	110	115

Average pressure, Erlanger, 129; Stanton, 128.

Table 5 would indicate that the readings of the cheaper instruments are practically the same as those of the Erlanger.

CONCLUSIONS

From a study of six hundred cases we draw the following conclusions:

1. The blood-pressure is increased at elevations of 6,000 feet.

2. The blood-pressure of both normal individuals and consumptives is higher at 6,000 feet than at sea level.

3. The pressure tends to increase up to certain limits with continued residence.

4. From a prognostic standpoint the blood-pressure findings are of great value in tuberculosis.

5. There is no relation between the degree of involvement and blood-pressure, but there is a constant relation between the degree of toxemia and blood-pressure.

"AURICULAR FLUTTER," WITH A REPORT OF TWO CASES *

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In 1911 Jolly and Ritchie[1] reported a case of Adams-Stokes disease which had been under observation for a period of six years and which showed in association with the complete heart-block a very rapidly beating auricle, the rate of the latter varying from time to time, but usually from 270 to 300 per minute. This condition they called auricular flutter. In adopting the term they refer to the work of McWilliams,[2] who, years ago, observed that the application of a faradic current started the auricle into a rapid flutter. In his account, McWilliams stated that the contractions originated in the stimulated area and extended rhythmically and coordinately throughout the tissue. In 1909, Hertz and Goodhart[3] reported a case with an auricular rate of 234 and a ventricular rate varying from 72 to 120. In this case the irregular and varying ventricular rate depended on a partial heart-block, although this was not recognized at the time. Lewis[4] has since written a very comprehensive article on the subject in which he reports eight cases which have come under his own observation and eight other cases which have appeared in the literature from time to time and which apparently are all types of this disorder. Ritchie[5] has also recently discussed the subject and reports four cases in which the condition has been definitely proved to be auricular flutter, and three others in which he believes that to have been the mechanism. These include the case reported in his original article. Hume's[6] case, no doubt, belongs in this category.

Auricular flutter when first described was considered a rare condition. As a matter of fact, it is probably comparatively common. The reason for its apparent rarity is that it is impossible to detect these extreme accelerations except by the use of graphic methods, and unless a routine examination by these methods is carried out many of the cases will escape recognition. The condition is an abnormal cardiac mechanism

* Read at the meeting of the American Climatological Association, Washington, D. C., May 6, 1913.
* Submitted for publication July 8, 1913.

1. Jolly and Ritchie: Heart, 1911, ii, 177.
2. McWilliams: Jour. Physicians, 1887, viii, 296.
3. Hertz and Goodhart: Quart. Jour. Med., 1909, ii, 213.
4. Lewis: Heart, 1912, iv, 171.
5. Ritchie: Edinburg Med. Jour., 1912, ix, 485.
6. Hume: Quart. Jour. Med., 1913, vi, 235.

characterized by a rapid, rhythmic, coordinate contraction of the auricle, the rate usually being somewhere between 200 and 300 per minute. A notable characteristic is the constancy in the auricular rate, any change due to posture or exercise being almost entirely negligible. Some degree of heart-block is usually present; consequently the ventricular rate is slower and may be regular or irregular.

It is a widely accepted belief that the normal cardiac impulse is brought about by a stimulus which arises in the sino-auricular node, sometimes called the pacemaker, situated near the mouth of the superior vena cava. This node gives rise to impulses in a healthy adult at the rate of about 72 to the minute. The rate is subject to wide variations as the result of exercise, emotion, fever and various other causes. The details of the mechanism which controls the rate are by no means clearly understood; whether the ordinary accelerations are due to diminished vagus tone or to direct stimulation through the sympathetic or to some other cause, it is not easy to prove, but, at any rate, it seems clear that all these simple accelerations are under the control of this mechanism whatever it is, and that all the impulses come from the normal point of origin. These have been called tachycardias of a physiological type, because they are simply the normal phenomenon exaggerated.

In auricular flutter the predominating evidence is that the origin of impulse is ectopic; that is to say, some other point than the normal pacemaker has taken on the function of stimulus production. It is well known that the ordinary premature auricular beat is the result of some pathological, usually ectopic, impulse formation. If a series of these beats arise in quick succession we recognize the condition clinically as paroxysmal tachycardia. This is usually characterized by a rate of 110 to 200 — rarely over 180. If, however, this abnormal focus in the auricle gives rise to impulses at a rate greater than 200, the condition has been called auricular flutter. This may seem an arbitrary division, for etiologically and pathologically it apparently does not differ from the simple paroxysmal type, but clinically it differs sufficiently so that it is considered advisable that it be classed in a separate category. It has been found, also, to have a close relation to auricular fibrillation, and when one considers the pathology and mechanism it is easy to see how readily a condition in which there is one abnormal point taking on the function of stimulus production might pass into a condition in which many foci have appropriated that function.

Some of the reasons for believing that the stimulus which gives rise to this action is ectopic in nature are as follows: 1. The already-mentioned close relation between this and the isolated premature auricular beat, the simple paroxysmal tachycardias and auricular fibrillation. 2. The auricular complex as recorded by the electrocardiograph

differs essentially from those which rise from the normal pacemaker. 3. The rhythm is not under nerve control as is the normal rhythm, being practically unaffected by posture, exercise or nerve stimulation.

The rate of the auricular beat varies considerably. In the cases collected by Lewis it has varied from 200 to 330 per minute. As already mentioned, this rate is remarkably constant, although observations made at long intervals of time show some variation in the rate. Observations made on the same day or on succeeding days usually show but little if any change.

The ventricular rate is usually slower, due to some degree of heart-block. The most frequent condition is a 2:1 ratio, in which the ventricle responds to each alternate auricular contraction. However, there may be any variation and instead of 2:1, the response may be at the ratio of 4:1. In either instance the ventricular rate is regular. If, however, as it is now known frequently occurs, the responses are mixed so that a 2:1, 3:1, 4:1, 5:1, etc., may be present, the pulse becomes entirely irregular and may be with difficulty distinguished from auricular fibrillation. The ratio of response may vary with exercise so that a patient who, lying down, would have a regular pulse at the ratio of 4:1, might, when standing, have a regular pulse with a 2:1 response, or a patient with a regular pulse with a ratio of 2:1 while active might have an irregular pulse because of mixed responses when at rest. In most of these cases the original grade of heart-block is increased by digitalis or strophanthus, which suggests that there is probably some impairment of muscle bundle conduction, for it is believed that these drugs have little, if any, influence on the conduction in a normal heart. Following the use of these drugs the regular 2:1 response may be converted into a condition of mixed responses of 2:1, 3:1, 4:1, 5:1. An interesting fact is that in the majority of instances these cases will pass from a 2:1 to a 4:1 ratio rather than from a 2:1 to a 3:1, and if the ventricle is irregular it is likely to consist of mixed 2:1 and 4:1 periods, though as Case 2 of those I am reporting shows, this is not always true. Isolated 3:1 or 5:1 periods may occur, but they are comparatively rare, and when a 3:1 ratio occurs successively the periods are usually short.

THE POLYGRAPHIC TRACINGS

The first case of Jolly and Ritchie, in which there was complete heart-block, and in which the jugular tracings were taken by a Knoll-Hering polygraph, showed distinctly the auricular waves. On the other hand, in many cases the jugular tracing is of no value in the diagnosis and may even be of such form as to be entirely misleading. In fact, the venous pulse in a 2:1 ratio is likely to be of the ventricular type. Occasionally when the ratio is 4:1 one may get an auricular wave toward the end of the ventricular pause and if, as sometimes happens, there is an

unusually prolonged pause there may be a series of auricular waves toward the end of it. Sometimes, as in one of my cases, the auricular waves are so prominent as to seriously complicate the c waves and in the attempt to identify the latter one may get a clue to the condition. The radial tracings are often of much more value in the analysis than the jugular and a close examination of the arterial pulse-curve alone may enable a positive diagnosis to be made. The points to be borne in mind as given in detail by Lewis are: 1. Alternation is commonly present. 2. The strength of the beats is substantially influenced by the preceding pauses. This is true, however, only when the pauses are too short for the ventricular contraction to be of maximal efficiency. 3. In the heart-block of flutter there is considerable variation in the As-Vs interval which modifies the expected pauses—a long pause is followed by a shortened conduction interval and a short pause by a lengthened conduction interval. 4. The weak beats are likely to be preceded by a relatively long presphygmic interval. All these factors must be considered, and contribute to the difficulties of the analysis. Usually when the ratio of ventricular response is irregular there is a definite grouping of beats, so that groups of three or four beats of irregular lengths may be repeated over and over again; but in some instances the ratio of response is so mixed that the condition is distinguished from fibrillation with difficulty.

TREATMENT

The general management of the case depends on the symptoms. If there is evidence of cardiac failure, of course, rest in bed is of paramount importance. The latter is just as beneficial in this condition as in any other in which the heart muscle is overtaxed. This was shown in Case 2 in which the patient had no medication for four days after admission to the hospital, but whose symptoms improved progressively from the time of admission though the pulse remained unchanged. Ordinary sedatives should be used as indicated in the individual case.

The particularly beneficial drugs, however, are digitalis and strophanthus. In several of the reported cases, during the administration of digitalis the flutter has passed into fibrillation. Then when digitalis is withheld the fibrillation has disappeared and the normal rhythm has become reestablished. Lewis explains this by saying that fibrillation seems to submerge the abnormal fast rhythm, which may not recur when the fibrillation passes off. As has already been stated, digitalis and strophanthus usually slow the heart by increasing the grade of heart-block so that these drugs may act beneficially in either of these two ways, namely, by causing fibrillation, which may subside, leaving the rhythm normal, or by slowing the pulse through increased heart-block.

In Case 2, digipuratum grs. 1½, was given four times a day for eight days. At the end of that time, as indicated by the tracing taken on March

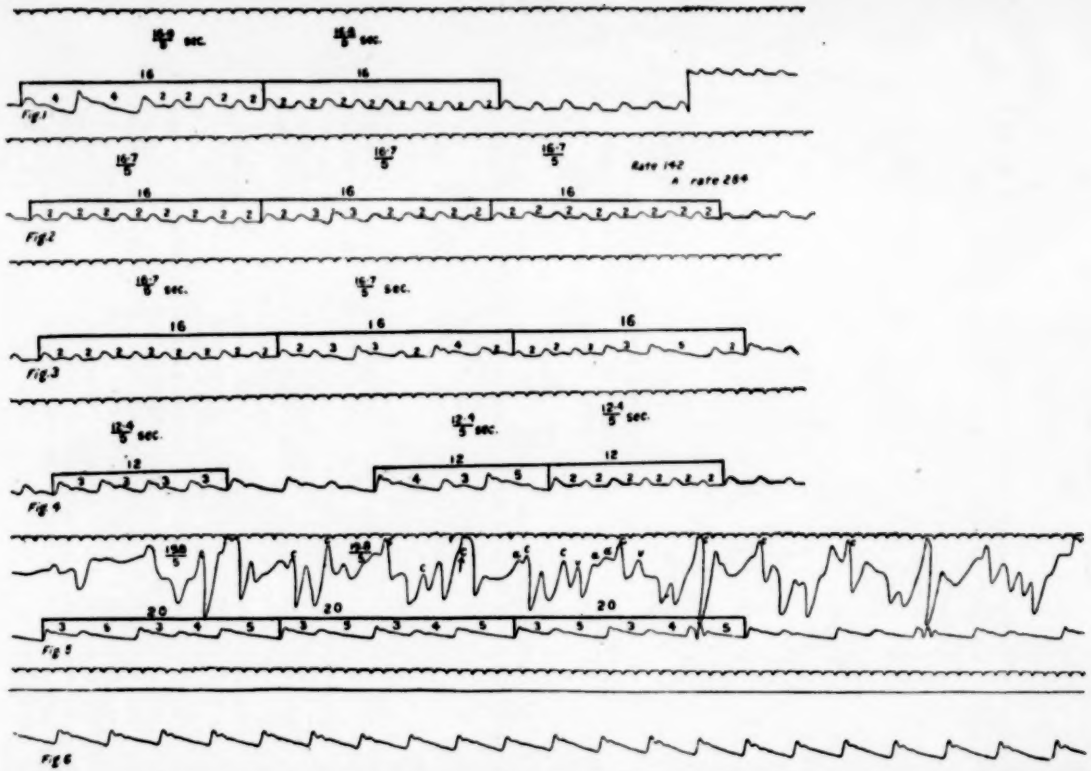
31, there was some increase in the grade of heart-block, causing a slowing of the pulse with some characteristic irregularity. What the dominant mechanism was during the next month is a matter of conjecture, but presumably flutter was persisting all this time, and on April 29 a tracing showed what appeared to be a 4:1 block. The amount of digitalis the patient had been having at that time is not definite. The patient was put on digitalis subsequent to this and a tracing taken on May 15 showed that the auricle had gone into fibrillation. The date on which this occurred is not known. Whether the fibrillation will be permanent or whether the normal rhythm will become reestablished, as frequently happens, can not at present be stated.

I shall report two cases, showing typical polygraphic tracings, which, when analyzed, leave no doubt that the mechanism present is that of auricular flutter. I have not been able to get electrocardiograms but have had to depend entirely on the polygraph.

CASE REPORTS

CASE 1.—Edwin C., aged 48, was admitted to the Rhode Island Hospital, Nov. 20, 1912, and came under my care Jan. 1, 1913. The patient is a native of Rhode Island and a jeweler by occupation. His family history is unimportant. He gives no history of any previous illness which might have any bearing on his present condition. He drinks considerable alcohol habitually, and occasionally to excess. A year before admission he began to get short of breath on exertion. About five weeks previous to my examination his legs began to swell and shortly before admission the swelling had extended to his hands, face and genitals. He had to get up at night to void urine occasionally. He was at work until within a week of his admission to the hospital. On admission there was slight swelling of all of the extremities and of the genitals, with some edema of the abdominal wall, but no definite signs of fluid in the abdomen. There were moist rãles in the bases of both lungs behind. Heart apex was in the fifth space 8 cm. from the mid-line and the organ was not definitely enlarged. Sounds were regular and clear, the aortic second slightly accentuated. The pulse was regular, of good volume and tension. Examination of the urine showed a trace of albumin with a moderate number of hyaline and granular casts. The quantity was rather scanty. The functional test with phthalein showed 20 per cent. efficiency. Patient had a good deal of dyspnea which came on periodically, some days being much less marked than others. It was relieved with morphin. His condition remained the same for a number of weeks, except that the edema of the extremities was increasing and the dyspnea was perhaps more marked. His pulse was noted frequently and was always regular. At the time of the morning visit, on the morning of February 10, it was noted to be rapid and irregular. A tracing of the arterial pulse was taken at that time, portions of which are shown in Figures 1 to 4, inclusive. These tracings show considerable stretches of an absolutely regular pulse at the rate of 143 per minute. Interspersed here and there in the tracing are irregularities of greater or less length. The evidence afforded by analysis is that the auricle is beating at the rate of 286 per minute and that the regular strips are a 2 : 1 response of the ventricle, while the irregularities are markedly irregular, the ratio of 2 : 1, 3 : 1, 4 : 1, 5 : 1, all being present.

While the dyspnea did not seem any more distressing with the onset of this irregularity, the edema did increase more rapidly after this rhythm was established and was relieved only by the use of Southey's tubes. In a tracing taken February 20 (Fig. 5) the irregularity was quite different, at this time a very



TRACINGS IN CASE 1.—Figures 1, 2, 3 and 4 are all a part of the same arterial tracing taken on the day the irregularity was first noticed. The short runs where the pulse is regular is a 2 : 1 block. The irregularities show ratios of 2 : 1, 3 : 1, 4 : 1 and 5 : 1. At one place in Figure 4 are four consecutive beats at the ratio of 3 : 1. The calculated auricular rate is 284.

Figure 5 was taken ten days after the onset. A group of five arterial beats of varying lengths recurs with great regularity. The estimated ratios here are 3 : 1, 5 : 1, 3 : 1, 4 : 1 and 5 : 1, giving an auricular rate of about 308. This, however, cannot be absolutely proven from the tracing. The jugular pulse shows chiefly ventricular waves.

Figure 6 was taken just after the normal rhythm was reestablished. It shows some sinus arrhythmia due to Cheyne-Stokes respiration.

definite grouping being quite persistent. For example, a group of five beats of varying lengths is repeated over and over again, the entire length of the group being $\frac{19.5}{5}$ seconds. The estimated ratio in these groups is 3 : 1, 5 : 1, 3 : 1, 4 : 1, 5 : 1, which would give an auricular rate on this day of about 308. Occasionally there is a break in this group.

This analysis of Figure 5 would seem most probably correct, though the evidence is not absolute.

The patient was given tincture of digitalis m. xv t.i.d. from February 20 to March 15. The irregularity continued until March 10, when it was noted at the morning visit that the pulse was regular. The tracing taken at that time showed the rhythm to be normal except for its modification from the Cheyne-Stokes breathing (Fig. 6). The patient is still in the hospital without any very material change in his condition. At times his dyspnea is marked and at times the Cheyne-Stokes breathing is marked, but there are other times when both of these are entirely absent. The edema is still quite considerable and although it cleared up materially with the return to the normal pulse rhythm, it is still necessary to remove some of it by Southey tube drainage.

SUMMARY OF CASE 1

A man of 48 suffering from progressive chronic nephritis with paroxysmal dyspnea and considerable edema, suddenly developed an irregular heart action after nearly three months in the hospital. This lasted for a month, when the rhythm suddenly became normal. There were no noticeable symptoms with the onset or end of the attack but the edema was considerably more marked while the condition persisted. Cheyne-Stokes breathing was present at the time of the return to the normal rhythm. Digitalis in moderate doses of the tincture was being administered during most of the time of the irregularity. The tracings indicate that the irregularity was due to a very rapidly beating auricle, associated with irregular ventricular responses.

CASE 2.—W. K., aged 54, was admitted to my service at the Rhode Island Hospital, March 17, 1913. The patient was a native of Rhode Island, a jeweler by occupation and came in complaining of shortness of breath and swelling of the legs. The physician who attended him before admission said that for a month his dyspnea had been marked and that it was with difficulty that he could go up even a slight incline. The trouble had been coming on gradually for a year but in November, 1912, he had an attack of bronchitis with a persistent and troublesome cough which aggravated the condition, so that there was increased shortness of breath, some swelling of the legs and considerable dizziness on exertion. He had to get up at night five or six times to void urine and was troubled a good deal with constipation. His general health, he stated, had always been good although he had had hay-fever in the summer for a number of years. On admission there was a good deal of dyspnea with orthopnea, some signs of a slight amount of fluid in the right chest and râles, with a distinct pleural friction. The heart was slightly enlarged and action very rapid but regular, there were no murmurs. His blood-pressure while in the hospital varied from 160 to 190. There was marked edema of both legs, with some dermatitis. The amount of urine averaged from 900 to 1,200 c.c. with a specific gravity from 1.009 to 1.012 showing a slight trace of albumin but no casts. The heart action was so rapid as to attract attention at once and a polygraph tracing was made. It showed a rate of 138 per minute, with marked alternation of the pulse. Patient, at first, received no medication. Two days later another tracing was taken showing a pulse rate of 136 and still with

marked alternation. The venous tracing on this day showed in places auricular waves at the rate of 272 per minute (Fig. 7). March 22, four days after admission, a third tracing was taken, showing the pulse rate 137. The patient had been in bed during the four days he had been in the hospital, but was at this time allowed to get up and was given some exercises at the side of the bed and a tracing was taken immediately afterward. The rate was absolutely unchanged. March 23 the patient was given digipuratum 1½ grs. four times a day. This was continued until March 31. The pulse was observed repeatedly and was always found to be regular, with the rate practically unchanged. The first irregularity was noted March 31 after eight days treatment with digitalis. A tracing made on that day shows a very interesting condition (Fig. 8). There are short runs of beats of the same length as had been present during all the time when he was under observation, but between these runs are periods of irregularity. Considering the condition while the pulse was regular to have been a 2 : 1 heart-block as evidenced by the venous tracing, analysis of the irregular curve shows a heart-block of a 2 : 1 ratio in the regular strips and mixed 2 : 1 and 3 : 1 ratios in the irregular strips. The irregularity is usually made up of groups of three beats, one of which is at the ratio of 2 : 1, the following two beats at the ratio of 3 : 1. In other words, when the pulse is regular there are four ventricular beats for every eight auricular beats, while in the irregular periods there are three ventricular beats for every eight auricular beats. The patient left the hospital on March 31, the day on which this tracing was made. He was not seen again until the afternoon of April 29. He had gone to work and had been able to work for a week. His old symptoms, however, returned so that he had to give up. The edema on this last date was again quite marked. He was sitting up in a chair and had spent several nights sitting up, not being able to sleep. He was having slight attacks of paroxysmal dyspnea. Cheyne-Stokes breathing of moderate type was present. The patient was able to move about the house without much evidence of shortness of breath. A tracing was taken which showed a regular pulse, rate 82 to the minute with slight alternation (Fig. 9). The tracing was continued at intervals for about an hour but at no time was there any irregularity whatever. The rate was absolutely constant. The patient twice got up from the chair, walked about the room and a tracing taken immediately after showed no change in the rate. The jugular tracing was not very satisfactory and while there were some extra small waves, there was nothing characteristic enough to make it absolutely sure whether the flutter is still persisting or not. The absolutely persistent rate unaffected by exercise suggests very strongly that the condition was still present and that there was a 4 : 1 block. Urinalysis: sp. gr. 1.020, trace of albumin, with a number of small hyaline casts. The patient was again seen May 15, when a tracing showed that the auricle had passed into fibrillation (Figs. 10 and 11).

SUMMARY OF CASE 2

A man aged 54, with gradually increasing dyspnea and edema for a year, comes under observation with chronic nephritis and an enlarged heart in stage of decompensation, and a pulse of 136 to 138 uninfluenced by posture or exercise. Auricular waves are present in the venous tracing at the rate of 272 per minute, indicating a 2:1 block. With rest in bed improvement was steady but the pulse was not slowed until after eight days of digitalis, when it became irregular, the latter being due to an increased grade of heart-block. Six weeks later the auricle was found to be in fibrillation.

Ritchie recognizes four groups of cases, the division being based on the symptomotology. These groups are as follows:

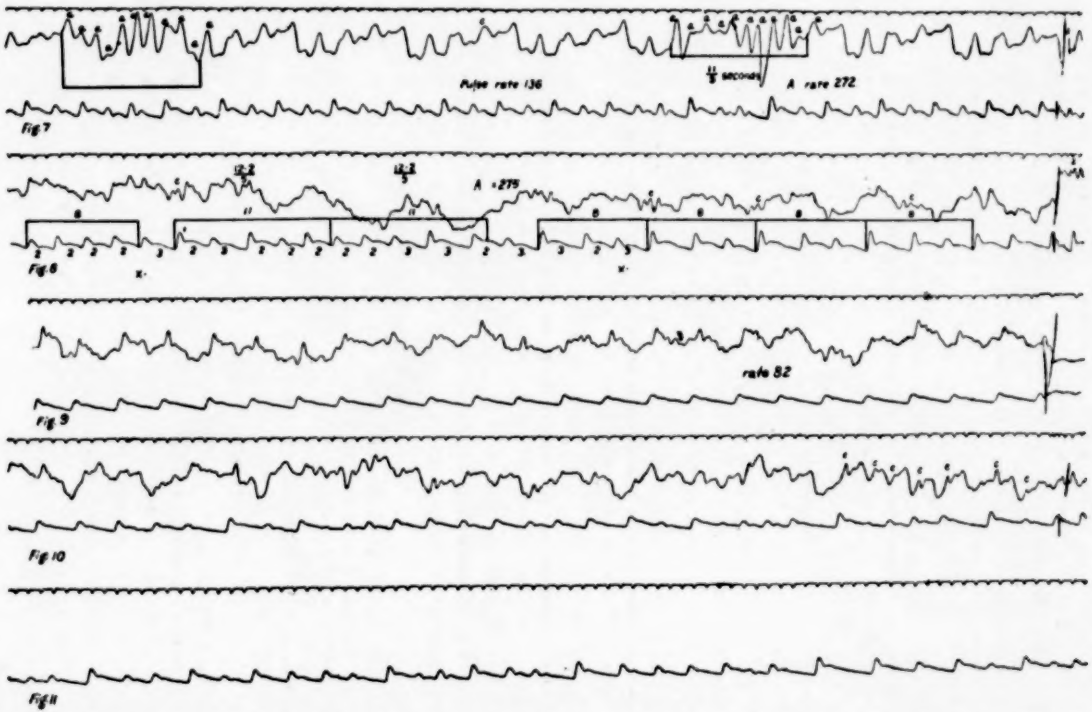


Fig 7

Fig 8

Fig 9

Fig 10

Fig 11

TRACINGS IN CASE 2.—Figure 7, two days after admission. The pulse is for the most part regular at a ratio of 2 : 1. At two points it suggests a 1 : 1 and 3 : 1 ratio. The auricular rate is 272. Alternation of the pulse is well marked.

Figure 8, after eight days of digitalis, showing mixed responses at 2 : 1 and 3 : 1 ratio, with short runs of 2 : 1. Patient left the hospital and was not observed for a month.

Figure 9, tracing made April 29, one month later. The pulse was regular, 82 to the minute, unaffected by posture and exercise.

Figures 10 and 11, taken May 15, show fibrillation.

1. Those in which there may or may not be signs of cardiac disorder but in which the symptoms are due to the rapid auricular and consequent rapid ventricular rate. It is perhaps in the cases of this group that the diagnosis of the condition is most difficult and also that it is of the most importance. For if there is no serious cardiac lesion and the auricles can be made to revert to their normal rhythm, the symptoms will quickly disappear and the patient may remain well for an indefinite period. Certain of the cases of this group, except for the greater rapidity of the auricular action, are hardly to be distinguished from ordinary paroxysmal tachycardia. The ratio of heart-block is likely to be 2:1 and unless some variation of this ratio occurs producing some irregularity, it may be impossible to arrive at a diagnosis from an analysis of the venous and arterial tracings. Persistent searching, however, is likely to discover some irregularity which may at once establish the diagnosis.

2. Cases of old standing cardiac disease in which the auricular tachycardia is apparently an incident in the progress of the disease. With the onset of flutter in these cases the condition usually becomes worse, as frequently happens with the onset of fibrillation.

3. Cases in which there is partial heart-block as a consequence of which the ventricular pulse is slow and likely to be irregular.

4. Auricular flutter associated with complete heart-block. In the latter, of course, the ventricular action is entirely unaffected by the rapid auricular rate.

It would seem reasonable to class the last two groups as one, inasmuch as the chief difference seems to depend on the grade of the impairment of conduction between the auricles and ventricles.

The two cases reported present certain points of similarity and would apparently fall into the second group mentioned by Ritchie. Both were near the end of the fifth decade of life. In each case there was some arterial hypertension, some chronic disease of the kidneys, some cardiac hypertrophy with cardiac insufficiency associated with dyspnea and edema. In one instance the onset of the abnormal rhythm and the reestablishment of the normal rhythm occurred while the patient was under treatment in the hospital. Tracings were not taken immediately before the rhythm returned to normal, so whether it passed through the stage of fibrillation is uncertain. The duration of the abnormal rhythm was about a month. In the other case, the auricle was in flutter when the patient came under observation. It passed into fibrillation about six weeks later and has remained in that state.